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ETIOLOGY AND TREATMENT OF SPRUE

OBSERVATIONS ON PATIENTS IN PUERTO RICO AND SUBSEQUENT EXPERIMENTS ON ANIMALS

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In 1759 William Hillary [1] described a peculiar chronic type of diarrhea associated with sore tongue, pallor and emaciation which he had observed in Barbados. Then for nearly a century there appear to have been no further distinctive clinical accounts of the disorder. In 1864 Julien [2] enunciated the view that "Cochin-China dysentery" was a specific condition different from other forms of dysentery. Despite his arguments and the views of other first-hand observers,[3] the French pathologists at home remained unconvinced. In 1880 both Manson,[4] in Amoy, and

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The observations on patients were carried out in 1931 by members of the Commission of the Rockefeller Foundation for the Study of Anemia in Puerto Rico; those on animals were performed subsequently at the Hospital of the Rockefeller Institute for Medical Research, New York.

From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital; the Department of Medicine and the Department of Tropical Medicine, Harvard Medical School; the Hospital of the Rockefeller Institute for Medical Research, and the Presbyterian Hospital, San Juan.

1. Hillary, William: Observations on the Changes of the Air and the Concomitant Epidemical Diseases in the Island of Barbadoes, London, C. Hitch & L. Hawes, 1759.

2. Julien, C. -M.: Aperçu sur les lésions anatomiques de la dyssentérie en Cochinchine, Montpellier, L. Christin & Cie., 1864.

3. Layet: Thèse de Montpellier, 1872. Laveran, A.: La diarrhée de Cochinchine, Bull. et mém. Soc. méd. d. hôp. de Paris **14**:71, 1877.

4. Manson, Patrick: Notes on Sprue, Medical Report, China Imperial Maritime Customs, Shanghai, 1879-1880.

van der Burg,[5] in Java, described the features of the disease which Hillary had observed. Each of these observers adopted as a scientific name for the disease its popular designation in Java. Since then the individuality of "sprue" has been established and its features have been described by many authors.

Various theories of the cause of the disease have been proposed. The original conflict between the theory of an infection and that of a deficiency origin has persisted. In 1884 Kiéner and Kelsch[6] claimed that in all cases of sprue there was an initial intestinal lesion from which the infection spread. Two years later the concept of deficiency disease was suggested by Maclean,[7] who reenforced the theory of Grant[8] that the stomatitis and aphthae were of scorbutic origin by stating that in order to effect a cure of the disease antiscorbutic remedies were required. In 1901 Kohlbrugge[9] gave definite impetus to the theory of an infectious origin by describing a yeast which he found in the feces as well as invading the mucous membranes of the intestinal canal. This lead was taken up by Castellani and Low,[10] Ashford,[11] Bahr[12] and others.[13] Ashford, working in Puerto Rico, became an enthusiastic exponent of the theory that the disease is due to a yeast, and in 1917 he described as the etiologic agent a species of Monilia which he claimed[14] to have found consistently on the tongue and in the feces of his patients. Ashford's views were, however, subsequently modified to admit the

5. van der Burg, C. L.: Indische Spruw (Aphthae tropicae), Batavia, Ernst & Company, 1880; translated in Medical Report, China Imperial Maritime Customs, Oct.-March, 1883.

6. Kiéner and Kelsch: Étude anatomo-pathologique de la dysentérie et recherches sur les nécroses expérimentales de la muqueuse intestinale, Arch. de physiol. norm. et path. **3**:186, 1884.

7. Maclean, W. C.: Diseases of Tropical Climates: Lectures Delivered at the Army Medical School, London, The Macmillan Company, 1886.

8. Grant, Alexander: Remarks on Hill Diarrhoea and Dysentery, Indian Ann. M. Sc. **1**:311, 1853-1854.

9. Kohlbrugge, I. H. F.: Een bijdrage tot de aetiologie der indische spruw (psilosis), Nederl. tijdschr. v. geneesk. **37**:881 (Oct. 19) 1901; Die Aetiologie der Aphthae tropicae, Arch. f. Schiffs- u. Tropen-Hyg. **5**:394, 1901.

10. Castellani, Aldo, and Low, G. C.: The Rôle Played by Fungi in Sprue, J. Trop. Med. **16**:33 (Feb. 1) 1913.

11. Ashford, B. K.: A Monilia Found in Certain Cases of Sprue: Preliminary Note, J. A. M. A. **64**:810 (March 6) 1915.

12. Bahr, P. H.: A Report on Researches on Sprue in Ceylon, 1912-1914, London, Cambridge University Press, 1915.

13. (*a*) Le Dantec, A.: Présence d'une levure dans le sprue: Sa signification pathogénique, Compt. rend. Soc. de biol. **64**:1066, 1908. (*b*) Wood, E. J.: Pernicious Anemia in Its Relationship to Sprue: A Preliminary Report, Am. J. M. Sc. **169**:28 (Jan.) 1925.

14. Ashford, B. K.: The Etiology of Sprue, Am. J. M. Sc. **154**:157 (Aug.) 1917.

basic factor of "nutritional unbalance."[15] Mackie and Chitre[16] have expressed the belief that there is no evidence to show that yeasts have a causative relation to sprue, and Mackie, Goré and Wadia[17] were unable to ascribe the disease to any recognized pathogenic bacteria.

The concept of sprue as a deficiency disease was again advocated in 1920 by Elders,[18] partly on the basis of McCarrison's[19] observations on the changes of the gastro-intestinal tract induced in experimental animals by feeding diets then considered to be deficient in vitamin B. The dietetic treatment naturally applied for the diarrhea of sprue was elaborated into a valuable regimen, but like the early dietetic treatment of scurvy or pellagra it was founded on an empiricism which suggested to very few a relationship to the cause of the disorder. In 1926 Minot and Murphy[20] announced a successful treatment for pernicious anemia consisting in a diet including large amounts of liver. Despite the fact that the liver extracts subsequently developed for the treatment of pernicious anemia by Cohn, Minot and their collaborators[21] were shown to be effective in the treatment of the macrocytic anemia of sprue in certain instances by Bloomfield and Wyckoff,[22] Richardson and Klumpp,[23] Ashford[24] and others,[25] this observation failed to modify

15. Ashford, B. K.: Observations on the Conception That Sprue Is a Mycosis Superimposed upon a State of Deficiency in Certain Essential Food Elements, Am. J. Trop. Med. **2**:139 (March) 1922.

16. Mackie, F. P., and Chitre, G. D.: (*a*) Yeasts and Sprue, Indian Medical Research Memoir, no. 11, Calcutta, Thacker, Spink & Company, 1928; (*b*) Animal Experiments and Sprue, Indian J. M. Research **16**:49 (July) 1928.

17. Mackie, F. P.; Goré, S. N., and Wadia, J. H.: The Bacteriology of Sprue, Indian J. M. Research **16**:95 (July) 1928.

18. Elders, C.: Over de proeven van McCarrison in verband met de opvatting, dat indische spruw een deficientieziekte is, Nederl. tijdschr. v. geneesk. **64**:2189, 1920.

19. McCarrison, Robert: Studies in Deficiency Disease, London, Henry Frowde & Hodder & Stoughton, 1921.

20. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926.

21. Cohn, E. J.; Minot, G. R.; Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia, J. Biol. Chem. **77**:325 (May) 1928.

22. Bloomfield, A. L., and Wyckoff, H. A.: The Treatment of Sprue with Liver Extract (343), Am. J. M. Sc. **177**:209 (Feb.) 1929.

23. Richardson, Wyman, and Klumpp, T. G.: Sprue: Report of a Case Treated with the Authorized Liver Extract Effective in Pernicious Anemia, New England J. Med. **199**:215 (Aug. 2) 1928.

24. Ashford, B. K.: The Anemias of Sprue: Their Nature and Treatment, Arch. Int. Med. **45**:647 (May) 1930.

25. (*a*) Suárez, R. M.: El tratamiento del esprú y el uso del extracto acuoso de hígado en su anemia, Bol. Asoc. méd. de Puerto Rico **23**:74 (March) 1931. (*b*) Suárez, J.: Pernicious Anemia and Sprue, Porto Rico J. Pub. Health & Trop. Med. **7**:145 (Dec.) 1931.

greatly the customary dietary treatment of sprue. This is difficult to understand in view of the fact that in an early paper Minot and Murphy [26] stated that the lingual and gastro-intestinal symptoms of pernicious anemia, like the anemia, were favorably affected by liver therapy. Moreover, liver soup had already been introduced by Manson in 1883 and used in the treatment of sprue for many years before the work of Minot and Murphy, as was stated by them.

With this background, our observations on sprue were begun under the auspices of the Rockefeller Foundation in Puerto Rico in 1931. A brief report [27] of the results has already been published. The present detailed report takes cognizance of certain subsequent observations made on patients and animals and so brings together evidence considered to indicate that sprue is primarily a deficiency disease closely allied to addisonian pernicious anemia and that substances present in extracts of liver effective in the treatment of pernicious anemia have a highly beneficial effect on all the major features of sprue.

METHODS

Observations were begun on over 100 patients with sprue and were satisfactorily carried out on 92. The patients were selected on the basis of symptomatology, such as sore tongue and diarrhea, or because they had definite anemia, usually of the macrocytic type. Thus, the group of patients included persons suffering both from the syndrome of "nutritional unbalance" of Ashford [28] and from fully developed and outspoken sprue with severe anemia. Most of the patients were adults. Patients with loss of blood or complicating infections were excluded as far as was possible. In several instances hookworm ova were found in the stools, and in a few cases the parasites were expelled at the completion of the observation. Experience with the anemia associated with hookworm infection indicated that, although the hookworm might have an influence in determining the type or degree of anemia, the results of effective therapy would not be greatly modified by their presence.[29]

The patients were observed either in the hospital or as visitors to a special clinic established at the Presbyterian Hospital in San Juan. Three of the patients were the subjects of special studies at the Thorndike Memorial Laboratory of the Boston City Hospital. Patients under observation in the hospitals, unless otherwise specified, were given a basal diet resembling as closely as possible the usual food of the Puerto Rican peasant. The major articles of this diet were rice, shell

26. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia: Study of One Hundred and Five Cases, J. A. M. A. **89**:759 (Sept. 3) 1927.

27. Castle, W. B., and Rhoads, C. P.: The Aetiology and Treatment of Sprue in Porto Rico, Lancet **1**:1198 (June 4) 1932; Observations on the Etiology and Treatment of Sprue in Puerto Rico, Tr. A. Am. Physicians **47**:245, 1932.

28. Ashford, B. K.: Sprue, in Tice, Frederick: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 4, p. 173. Ashford.[15]

29. Rhoads, C. P.; Castle, W. B.; Payne, G. C., and Lawson, H. A.: Obsercations on the Etiology and Treatment of Anemia Associated with Hookworm Infection in Puerto Rico, Medicine **13**:317 (Sept.) 1934.

beans and white bread, such tropical vegetables as *yautía, ñame* and *plátano* and the juices of citrous fruit. Meat and eggs were not given. A small amount of milk was permitted in coffee. Salt and sugar were given as desired. Carbohydrate desserts with syrup were freely used. The quantity of the diet was limited only by the desire of the individual patient for food. Numerous control periods of observations showed that the symptoms and blood picture of the patients were never significantly improved by this basal regimen. In the management of outpatients suggestions as to diet were never made. Usually a general history, and in 63 instances a dietary history, was taken, and a physical examination was carried out. The blood was examined for malaria in all doubtful cases, and the Kahn test for syphilis was always performed. Biopsies of the sternal bone marrow were made on 22 patients at various stages of the anemia. Gastric analyses were performed on 65 patients. Systematic culture of the stools of 56 patients for yeastlike organisms was made and controlled with similar observations on a series of 46 patients with hypochromic anemia associated with hookworm infection.

The hematologic studies were made on 5 cc. samples of venous blood drawn without stasis and rendered incoagulable by 0.05 cc. of a 20 per cent solution of potassium oxalate. Since the factors of dilution and shrinkage of the cells were small and constant, no corrections were made for them. The corpuscular counts were made by the usual technic with certified apparatus. The percentage of hemoglobin was determined with a single Sahli instrument with a solid standard. One hundred per cent was considered equivalent to 15.6 Gm. per hundred cubic centimeters of blood. The indexes of mean corpuscular volume and of hemoglobin were calculated from uncorrected hematocrit values determined by the method of Wintrobe.[30] The color of the serum was estimated with bichromate standards according to the method of Murphy,[31] and the bilirubin content of the serum was determined by the well known quantitative method of van den Bergh. Blood films were made on coverglasses previously coated with brilliant cresyl blue in order to stain the reticulocytes supravitally before the films were counterstained with Wright's stain. When a patient was in the hospital a 5 cc. sample of venous blood was usually taken every other day, and reticulocyte counts were made daily. For outpatients samples of venous blood were examined at intervals of one or two weeks.

The plan of study included the descriptive observations just mentioned and determinations under controlled conditions of the effect of various procedures, especially on the formation of blood. Previous experience with a few cases of sprue observed in Boston had suggested certain significant etiologic relationships between the anemia of sprue and that of addisonian pernicious anemia. Attempts were therefore made to evaluate the relative importance of dietary deficiency, specific changes in the gastric contents and disturbances of the absorption of hematopoietic substances. In view of the work of Bloomfield and Wyckoff,[22] Ashford,[24] R. M. and J. Suárez [25] and others [23] on the effects of extracts of liver known to be potent in the treatment of pernicious anemia, studies of the therapeutic value of liver extracts administered both orally and parenterally [31a] were carried out.

30. Wintrobe, M. M.: The Volume and Hemoglobin Content of the Red Blood Corpuscle: Simple Method of Calculation, Normal Findings, and Value of Such Calculations in the Anemias, Am. J. M. Sc. **177**:513 (April) 1929.

31. Murphy, W. P.: An Easy Method of Estimating the Amount of Jaundice by Means of the Blood Serum, Boston M. & S. J. **194**:297 (Feb. 18) 1926.

31a. Unless otherwise specified, liver extract-Lilly, N. N. R., supplied by the manufacturer, was used for oral administration. The product for parenteral use was prepared by us from this substance.

As far as can be ascertained, except for a patient previously treated [32] in Boston, these were the first observations on the parenteral use of liver extract in the treatment of sprue.[27] The effects on the formation of blood of a dietary regimen for sprue and of preparations of autolyzed yeast were compared with those of liver extract therapy. The accessory value of iron therapy was also determined.

The immediate effect of these procedures on the formation of blood was determined by daily observations of the course taken by the reticulocyte count. This index has been applied to the study of both macrocytic and hypochromic anemia.[33] It permits the detection of hematopoietic activity within from ten to fourteen days and affords a basis of comparison in the same patient of the hematopoietic effects of different substances. The principles of this test in pernicious anemia have recently been reviewed by Minot.[34] Here it suffices to say that from the uniform daily administration of hematopoietically active substances to patients with less than 3,000,000 red blood cells per cubic millimeter an increase in the reticulocyte count may be expected to appear before the tenth day and reach a "peak" value usually about the seventh day, rarely as late as the fourteenth day, after the initiation of therapy. The peak value is roughly proportional to the amount of active substance administered up to a given maximal dosage of the active material. The peak value of the reticulocyte count is also roughly inversely proportional to the initial level of the erythrocyte count. If in response to the uniform daily administration of an active substance a submaximal reticulocyte value has occurred and is on a decline, the immediately subsequent uniform daily administration of a larger amount of active material may produce a second peak of the reticulocyte count higher than, equal to, or lower than, the first. The relative magnitude of the second peak will depend on how much greater than the activity of the first material was the activity of the second material administered. On these principles are based many of the observations on the patients with sprue to be described later. In addition, the effect of certain procedures on the values for red blood cells and hemoglobin was determined.

OBSERVATIONS CONCERNING THE ETIOLOGY OF SPRUE

DESCRIPTIVE OBSERVATIONS

Excellent descriptions of sprue have been recorded by clinicians whose experience has been far more extended than ours. The following

32. Strauss, M. B., and Castle, W. B.: Parenteral Liver Therapy in the Treatment of Pernicious Anemia, J. A. M. A. **98**:1620 (May 7) 1932.

33. (*a*) Minot, G. R.; Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy, Particularly in Pernicious Anemia, Am. J. M. Sc. **175**:581 (May) 1928. (*b*) Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract: Effects upon the Production of Immature and Mature Red Blood Cells, ibid. **175**:599 (May) 1928. (*c*) Bethell, F. H., and Goldhamer, S. M.: Standards for Maximum Reticulocyte Values Following Ventriculin and Intravenous Liver Extract Therapy in Pernicious Anemia, ibid. **186**:480 (Oct.) 1933. (*d*) Minot, G. R., and Heath, C. W.: The Response of the Reticulocytes to Iron, ibid. **183**: 110 (Jan.) 1932.

34. Minot, G. R.: The Interpretation of Reticulocyte Responses in Pernicious Anemia, Tr. A. Am. Physicians **49**:287, 1934. Minot, G. R., and Castle, W. B.: The Interpretation of Reticulocyte Reactions: Their Value in Determining the Potency of Therapeutic Materials, Especially in Pernicious Anemia, Lancet **2**:319 (Aug. 10) 1935.

descriptions of the clinical features, the blood picture and the bone marrow in cases of sprue, however, may be of value because presented by observers to whom, although the clinical study of sprue was essentially new, other types of severe anemia were familiar. A deliberate attempt was therefore made not to become involved in a study of the minute details of the clinical picture so well done by others. Rather, it was our object to compare the chief manifestations of sprue with the corresponding features of other diseases with gastro-intestinal symptoms and signs in which anemia is a common finding.

The Clinical Picture.—In his classic description of sprue Manson [35] divided the patients into two groups: those with "complete" and those with "incomplete" sprue. The latter designation was applied to those patients in whom there were no symptoms referable to the tongue and mouth and in whom intestinal symptoms predominated. In 1915 Bahr [12] added a third division of the cases by including patients suffering from "tongue or mouth" sprue. In these patients symptoms referable to the tongue and mouth may be present for years without other features of the fully developed disease. Ashford [28] apparently classified under his syndrome of "nutritional unbalance preceding sprue" the groups of incomplete and tongue-and-mouth sprue. His vivid description of this state was based on years of observation. It apparently corresponds to the condition of only about 16 of our 92 patients. In a recent article Manson-Bahr and Willoughby [36] classified 22 per cent of their 200 cases under incomplete sprue. Since it was our object to examine patients mainly with the fully developed disease and anemia or patients who presented definite lingual changes, many patients with suspicious early sprue of this type were not admitted for study. It is our impression that the asthenia, sore and "inflamed" tongue, copious foamy stools and emaciation were stages of variable duration of a disorder of an irregularly progressive character. The symptoms of the incomplete disease were often those which had been presented for a short time by the patient with fully developed sprue. For this reason the dynamic rather than the static picture of the symptomatology is, as implied by Ashford,[28] essential to a depiction of the disease.

Certain writers have noted the occurrence of symptoms and signs suggestive of neurologic involvement in sprue clinically [37] and at post-

35. Manson, Patrick: Sprue, in Allbutt, C., and Rolleston, H. D.: A System of Medicine, New York, The Macmillan Company 1907, vol. 2, p. 545. Manson.[4]

36. Manson-Bahr, Philip, and Willoughby, Hugh: Studies on Sprue with Special Reference to Treatment: Based upon an Analysis of Two Hundred Cases, Quart. J. Med. **23**:411, 1930.

37. (*a*) Hance, J. B.: Notes on the Pathogenesis of Sprue and the Asthenic Diarrhoea of Indians, Indian M. Gaz. **65**:125 (March) 1930. (*b*) Baumgartner, E. A., and Smith, G. D.: Pernicious Anemia and Tropical Sprue, Arch. Int. Med. **40**:203 (Aug.) 1927. (*c*) Wood.[13b]

mortem examination.[38] Suspicious signs of mild forms of this condition were observed in 8 of the 92 patients of this series. The symptoms are not to be confused with the frequent and inconstant cramps of the muscles or transitory numbness and coldness of the hands and feet. These patients exhibited a definite instability of locomotion and complained of constant symmetrical paresthesia in the hands or feet. Some diminution of the sense of vibration of the ankles was present in all; in 3 patients the knee jerks were greatly diminished, but in none was the Babinski phenomenon present. Aside from this our observations of the clinical features of the cases studied in Puerto Rico bear out the excellent recent clinical descriptions of Manson,[35] Ashford,[28] the Bahrs,[39] Baumgartner [37b] and others.[40]

The Blood Picture.—The blood picture in sprue has frequently been described and the resemblance of the macrocytic anemia to pernicious anemia pointed out.[41] Ashford [28] found that about half of his severely anemic patients in Puerto Rico showed a "secondary" type of anemia. Fairley, Mackie and Billimoria [42] found that over half of their 67 patients had a color index of 1 or more. Baumgartner [43] stated that of 36 patients 16 had anemia with a high color index. All these authors have emphasized the large size of the red cells as measured by the technic of Price-Jones [44] in those patients whose blood showed a high color index. They have agreed that the white blood cells have a tendency to be decreased in numbers with relative lymphocytosis in the patients with the lower red blood cell counts. Baumgartner found the Arneth count of value in distinguishing the anemia of sprue from that of pernicious anemia since the lobulations of the neutrophils in a person with sprue resemble more nearly those in the blood of a normal person. Few observations of the platelets have been recorded. Fairley, Mackie and Billimoria found that the bilirubin content of the blood was not increased so constantly as in cases of pernicious anemia with relapse. Otherwise the blood picture found by these authors in many instances appears to be indistinguishable from that of pernicious anemia.

38. Reed, A. C., and Wyckoff, H. A.: The Common Picture of Sprue, Pernicious Anemia, and Combined Degerenation, Am. J. Trop. Med. **6**:221 (May) 1926.

39. Manson-Bahr and Willoughby.[36] Bahr.[12]

40. Musser, J. H.: Clinical Manifestations of Sprue and Relation of the Disease to Pernicious Anemia, M. Clin. North America **9**:895 (Jan.) 1926.

41. Reed and Wyckoff.[38] Musser.[40] Wood.[15b]

42. Fairley, N. H.; Mackie, F. P., and Billimoria, H. S.: Anaemia in Sprue: An Analysis of Sixty-Seven Cases, Indian J. M. Research **16**:831 (Jan.) 1929.

43. Baumgartner, E. A.: The Blood Picture in Tropical Sprue, Folia haemat. **43**:192, 1930.

44. Price-Jones, Cecil: The Diurnal Variation in the Sizes of Red Blood Cells, J. Path. & Bact. **23**:371, 1920.

The findings in the blood of our series of 92 patients are perhaps not comparable to those of other observers since the patients were especially selected for study because they had severe anemia of the macrocytic type. Ashford [45] has reported the occurrence of lingual and gastrointestinal symptoms in patients regarded as suffering from hookworm disease. Such symptoms were frequently observed in our series of patients with hypochromic anemia and hookworm infection.[29] These similarities indicate the difficulty of distinguishing, on a symptomatic basis, certain patients with hookworm disease from others with sprue. Conversely, several of the patients here included as having sprue were carriers of the hookworm, although most of them did not have the hypochromic type of anemia usually associated with infection with that parasite. With these reservations, the individual blood pictures on the first examinations of our 92 patients regarded as suffering from sprue are set forth in table 1 and are summarized in table 2 with respect to initial values of red blood cells, white blood cells, color index, mean corpuscular volume, mean concentration of corpuscular hemoglobin and icterus index. With the particular technic employed the average indexes for cell volume and concentration of hemoglobin of Wintrobe [30] determined on four different occasions on 5 normal subjects were: for mean corpuscular volume, 84.8 cubic microns, and for mean concentration of corpuscular hemoglobin, 34.3 per cent. Because these figures were uncorrected for cell shrinkage they vary slightly from the average corrected values given by Wintrobe.

In general the blood picture was that of macrocytic anemia, although in cases 11, 28, 29, 41, 84 and 87 the picture assumed a definitely hypochromic character and in cases 11 and 87 it was also microcytic. In cases 28 and 84 hookworm ova were found in the stools. Marked variation in the size and shape of the erythrocytes, with many oval cells and occasional primitive nucleated cells, was noted in severely anemic patients. Leukopenia, often with relative lymphocytosis, and diminution of the blood platelets were noted in stained films. These observations confirm those of others and show that the blood picture is similar to that of addisonian pernicious anemia.

The blood picture of sprue, however, has been stated to differ from that of pernicious anemia in that the anemia in the latter condition is more regularly macrocytic [46] and the frequency of an elevated content of serum bilirubin greater.[42] In table 2 are summarized the major features of the initial blood findings in the 92 patients with sprue as compared with the findings in 40 patients with pernicious anemia, mainly in the first relapse, who were admitted consecutively to the Harvard medical

45. Ashford, B. K.; King, W. W., and Gutiérrez Igaravídez, P.: Report of the Study and Treatment of "Anemia" in Porto Rico, San Juan, Puerto Rico, Bureau of Printing and Supplies, 1904.

46. Ashford.[28] Baumgartner.[43]

TABLE 1.—*The Initial Blood Findings, Duration and Type of Symptoms, Results of Gastric Analysis and Observations for Yeastlike Organisms and Hookworm Ova in the Stools of 92 Patients with Sprue*

Case	Sex	Age, Years	Red Blood Cells, Millions	Hemoglobin, per Cent	White Blood Cells, Thousands	Reticulocytes, per Cent	Color Index	Mean Corpuscular Volume, Cubic Microns	Mean Concentration of Corpuscular Hemoglobin, per Cent	Icterus Index	Symptoms				Gastric Analysis*	Stools		
											Duration	Tongue	Diarrhea	Nerve		Yeast Cultures: Positive	Yeast Cultures: Negative	Hookworm Ova, per Cg.
1	M	46	3.52	78	3.3	0.4	1.10	110	31	4	5 yr.	+	0	+	0	..	..	0
2	F	25	1.56	32	4.8	3.4	1.02	108	30	2	9 mo.	+	+	0	hist.	..	2	12
3	F	56	3.73	78	3.5	1.0	1.04	99	33	..	2 yr.	+	0	0	alc.	..	2	0
4	M	55	2.26	55	5.6	3.2	1.22	125	30	2	.....	+	+	0	alc.	..	1	117
5	M	22	1.56	44	6.2	1.4	1.82	136	32	3	3 mo.	+	0	0	alc.	..	2	0
6	M	53	1.92	47	5.7	1.2	1.22	118	32	7	.....	..	..	..	.....	..	..	0
7	F	55	3.60	82	8.7	1.6	1.14	104	34	3	.....	..	..	..	.....	..	..	..
8	F	63	1.22	32	2.9	0.8	1.31	120	34	12	4 yr.	+	0	0	.....	..	..	0
9	F	47	2.15	55	6.7	1.4	1.27	128	31	3	10 mo.	+	+	0	hist.	5	1	0
10	M	29	2.39	67	3.0	1.0	1.40	129	34	3	15 yr.	+	+	0	alc.	3	..	0
11	F	33	4.66	50	10.4	2.2	0.54	61	27	2	5 yr.	+	+	0	.....	2	..	0
12	F	41	2.20	64	7.1	0.5	1.45	137	33	2	18 mo.	+	+	0	hist.	2	..	0
13	M	60	2.67	65	6.7	...	1.22	114	33	3	.....	..	..	..	.....	..	..	..
14	M	45	2.46	60	5.6	0.8	1.22	114	33	6	2 yr.	..	..	+	.....	..	..	..
15	M	60	1.80	50	7.8	4.2	1.39	135	32	5	10 yr.	+	+	0	alc.	..	5	0
16	F	40	1.94	43	5.6	1.0	1.11	112	31	4	.....	+	..	..	hist.	3	2	0
17	F	12	2.56	75	3.6	1.2	1.46	127	36	4	.....	..	..	..	alc.	..	1	0
18	M	48	2.80	71	3.5	0.8	1.27	114	35	8	4 yr.	+	+	0	.....	..	..	0
19	M	48	1.55	36	4.6	0.6	1.16	111	33	3	1 yr.	+	+	0	0	..	1	+
20	M	35	2.67	68	7.1	1.2	1.27	120	33	5	4 yr.	+	+	0	.....	..	..	0
21	M	49	2.30	70	3.8	1.2	1.52	145	33	2	2 yr.	+	+	0	hist.	1	..	..
22	M	69	1.98	56	5.6	0.8	1.41	140	31	2	1 mo.	+	+	0	0	..	4	..
23	M	68	1.63	42	8.5	1.8	1.29	132	31	8	3½ yr.	+	+	0	alc.	1	..	0
24	F	51	2.67	54	8.5	1.0	1.01	110	29	3	.....	+	+	0	.....	..	..	..
25	M	42	2.51	78	4.8	1.6	1.55	141	35	3	.....	+	..	..	.....	..	..	..
26	F	44	3.18	64	2.2	0.4	1.00	105	30	4	4 yr.	+	+	0	alc.	..	1	0
27	F	59	1.39	48	3.9	0.6	1.27	166	32	6	12 yr.	+	+	0	.....	..	..	..
28	M	30	0.83	14	2.5	3.6	0.84	92	29	4	8 mo.	+	+	0	alc.	1	1	586 worms
29	M	63	3.68	67	4.2	0.4	0.91	90	32	3	4 mo.	+	+	0	hist.	..	1	..
30	F	60	1.30	33	3.8	2.4	1.27	132	30	6	3 mo.	+	+	0	0	4	..	7
31	M	20	1.28	49	2.1	4.0	1.91	154	39	30	8 yr.	+	+	0	0	1	1	328
32	F	72	1.23	31	4.2	0.8	1.26	120	33	30	2 yr.	+	+	0	alc.	..	..	0
33	F	66	1.48	45	3.5	1.4	1.52	153	31	3	2 yr.	±	+	0	.....	..	..	..
34	F	65	2.33	57	4.5	4.8	1.22	113	34	3	.....	+	+	0	alc.	3	1	0
35	M	65	1.76	49	2.4	0.8	1.39	132	33	6	10 yr.	+	+	0	0	2	8	24
36	M	22	1.94	45	4.5	3.0	1.16	111	33	5	10 yr.	+	+	0	alc.	..	..	0
37	M	67	1.92	42	4.0	1.4	1.09	104	33	3	2 yr.	+	+	0	0	2	4	0
38	F	35	3.11	75	6.2	1.2	1.20	119	32	3	.....	..	..	..	alc.	..	1	..
39	M	58	2.00	58	4.5	0.8	1.45	141	32	4	7 yr.	+	+	0	0	1	..	0
40	M	62	1.54	47	5.0	3.6	1.53	133	36	8	5 yr.	+	+	0	hist.	..	1	0

41	M	54	3.81	72	5.5	1.0	0.94	98	30	5	.....	+	..	..	.....	..	..	..
42	M	18	2.18	63	7.1	0.8	1.44	135	33	3	3 yr.	+	+	0	ale.	..	..	4	66
43	M	27	0.55	17	2.6	0.6	1.54	151	32	15	4 mo.	0	+	0	.....	..	..	..	0
44	F	59	0.89	22	3.5	3.2	1.24	126	31	20	5 yr.	+	+	0	0	1	..	..	0
45	M	63	2.23	57	4.9	3.2	1.28	117	34	20	4 mo.	0	0	0	0	..	..	..	0
46	F	50	3.27	74	6.1	1.0	1.13	112	32	2	.....	..	..	..	.....	..	..	..	..
47	F	75	1.58	48	3.8	1.2	1.52	144	33	20	.....	..	..	..	ale.	..	2	0	
48	M	46	2.78	73	8.4	0.4	1.31	121	34	5	18 mo.	+	+	0	.....	1	..	..	
49	M	75	0.57	18	1.7	1.0	1.57	142	35	15	6 mo.	+	+	0	0	..	3	..	
50	F	55	3.45	79	4.3	2.4	1.14	102	35	6	20 yr.	+	+	0	ale.	..	..	0	
51	M	35	0.68	20	2.5	1.8	1.47	124	37	8	6 mo.	+	+	0	0	1	1	0	
52	F	40	2.76	56	15.6	6.8	1.00	97	33	9	5 yr.	+	+	0	ale.	..	2	0	
53	M	44	1.39	41	4.1	1.2	1.47	132	35	20	1 mo.	+	+	0	0	2	2	0	
54	F	80	1.13	29	7.4	0.8	1.28	120	34	10	7 mo.	+	+	+	0	2	2	..	
55	F	32	1.72	56	5.4	2.0	1.63	162	31	3	3 mo.	0	+	0	hist.	..	..	..	
56	F	52	1.67	50	5.8	5.2	1.47	156	30	3	2½ yr.	+	+	0	ale.	..	1	0	
57	F	67	1.07	27	2.4	3.4	1.26	124	32	4	2½ yr.	+	+	0	0	..	..	..	
58	M	61	2.34	64	4.4	1.6	1.39	132	32	10	4 yr.	+	±	+	.....	..	..	..	
59	F	35	1.04	23	2.3	1.2	1.10	114	30	25	.....	..	..	..	hist.	1	1	0	
60	M	65	3.12	73	7.5	1.6	1.16	112	33	3	9 yr.	+	+	+	0	3	3	0	
61	M	60	1.01	27	2.3	2.0	1.33	123	34	6	8 yr.	+	+	0	ale.	1	..	136	
62	F	45	2.22	63	7.2	3.0	1.42	136	33	8	.....	..	..	0	.....	..	..	0	
63	M	40	2.65	83	6.4	0.4	1.57	146	34	3	.....	+	+	0	.....	..	1	0	
64	F	52	1.61	34	2.4	2.8	1.06	97	34	10	5 yr.	+	+	0	ale.	..	..	0	
65	F	62	0.93	25	2.5	0.8	1.34	136	31	15	2 yr.	+	+	0	hist.	..	1	0	
66	M	45	2.45	75	5.3	0.6	1.53	142	34	3	13 yr.	+	+	+	.....	..	..	..	
67	F	80	2.81	67	4.6	1.0	1.19	108	35	2	8 mo.	+	+	0	.....	..	..	..	
68	M	58	1.32	47	4.1	3.6	1.78	159	35	4	2 yr.	+	+	+	ale.	..	1	0	
69	F	35	2.90	78	11.0	1.4	1.34	127	33	6	3 yr.	+	0	0	.....	..	..	..	
70	M	55	2.85	77	6.8	1.4	1.35	129	33	2	20 yr.	+	+	+	ale.	..	1	0	
71	F	70	1.91	60	4.3	1.4	1.53	148	33	10	.....	..	..	..	.....	..	..	0	
72	M	24	1.16	29	6.2	1.2	1.25	119	33	5	3 yr.	+	+	0	0	..	1	+	
73	F	50	1.33	36	4.9	2.0	1.35	122	35	25	2 yr.	+	±	0	.....	1	..	0	
74	M	55	1.23	35	4.2	1.0	1.42	133	34	7	4 yr.	+	+	0	ale.	..	1	0	
75	M	52	0.89	28	2.0	1.6	1.57	134	37	12	2 yr.	+	+	0	0	2	1	67	
76	M	34	1.18	33	4.3	2.4	1.39	134	33	10	10 mo.	+	+	0	hist.	2	..	+	
77	M	66	2.66	67	3.0	2.0	1.26	118	33	3	3 mo.	+	+	0	.....	..	1	0	
78	F	46	0.90	28	1.8	1.4	1.55	148	33	4	4 yr.	+	0	0	.....	..	..	..	
79	M	50	1.56	39	6.7	2.4	1.25	113	35	3	4 yr.	+	+	0	ale.	1	1	96	
80	M	33	2.74	68	3.1	0.4	1.24	109	36	15	1 yr.	+	+	0	ale.	1	1	0	
81	M	62	0.94	24	4.5	2.2	1.29	109	37	30	6 yr.	±	0	0	0	..	..	..	
82	M	54	1.02	29	2.4	3.0	1.42	140	32	6	2 yr.	+	+	0	ale.	..	1	0	
83	F	62	1.08	29	4.4	3.0	1.34	117	36	50	4 yr.	+	+	0	ale.	..	1	0	
84	F	42	2.95	52	4.8	0.8	0.88	86	32	3	16 yr.	+	+	0	hist.	1	1	14	
85	M	46	2.81	75	4.9	0.4	1.33	126	33	5	5 mo.	+	+	0	ale.	..	..	4	
86	F	52	2.24	68	4.0	0.4	1.52	117	34	4	2 yr.	+	+	0	ale.	..	..	..	
87	F	35	3.81	44	6.0	0.6	0.58	65	28	2	2 yr.	+	+	0	0	..	1	0	
88	M	10	1.42	47	5.0	7.2	1.65	151	34	3	.....	+	..	..	ale.	..	..	..	
89	F	28	3.02	66	4.8	1.6	1.09	103	33	2	.....	+	..	..	.....	..	1	0	
90	M	60	2.24	52	5.1	0.8	1.16	...	..	..	10 yr.	+	+	0	ale.	..	..	0	
91	M	86	3.92	80	4.1	...	1.02	101	32	..	1 yr.	0	+	0	ale.	..	..	0	
92	M	54	1.51	39	2.7	1.6	1.29	104	39	..	7 yr.	+	+	0	ale.	..	..	0	

* Ale. indicates the secretion of free hydrochloric acid after the administration of 50 cc. of 7 per cent alcohol; hist., after the injection of 0.5 mg. of histamine phosphate; 0, indicates no secretion of hydrochloric acid.

services of the Boston City Hospital during the past two years. It is clear that the resemblances between the blood findings of the two groups are striking. The patients with pernicious anemia had, on the average, a greater degree both of anemia and of leukopenia. The mean concentration of corpuscular hemoglobin was more than 34 per cent in a greater percentage of the patients with pernicious anemia. On the other hand, the percentage of patients with a color index greater than

TABLE 2.—*Comparison of Initial Blood Values of 92 Patients with Sprue with Those of 40 Patients with Addisonian Pernicious Anemia* *

	Erythrocytes, Millions per Cu. Mm.				
	0 to 0.9	1 to 1.99	2 to 2.99	3 to 3.99	4 to 4.99
Sprue	9.8	41.3	33.7	14.1	1.1
Pernicious anemia	7.5	62.5	25.0	5.0	0

	Leukocytes, Thousands per Cu. Mm.			
	<3	3 to 4.9	5 to 6.9	>7
Sprue	18.5	42.4	23.9	15.2
Pernicious anemia	35.0	47.5	15.0	2.5

	Color Index						
	<0.6	0.6 to 0.79	0.8 to 0.99	1 to 1.19	1.2 to 1.39	1.4 to 1.59	>1.6
Sprue	2.2	0	4.4	21.7	38.0	28.3	5.4
Pernicious anemia	0	0	5.0	40.0	50.0	2.5	2.5

	Mean Corpuscular Volume, Cubic Microns (Normal, 84.8)							
	<80	80 to 89	90 to 99	100 to 109	110 to 119	120 to 129	130 to 139	140 to 149	>150
Sprue	2.2	1.1	6.6	12.1	21.9	18.7	16.5	12.1	8.8
Pernicious anemia	0	2.5	10.0	32.5	22.5	25.0	7.5	0	0

	Mean Concentration of Corpuscular Hemoglobin, Percentage (Normal, 34.3)							
	<29	29	30	31	32	33	34	>34
Sprue	2.2	2.2	7.7	9.9	15.4	27.4	15.4	19.8
Pernicious anemia	0	7.5	5.0	7.5	15.0	10.0	20.0	35.0

	Icterus Index, Units (Normal, 6)		
	<6	6 to 10	>10
Sprue	58.0	22.7	19.3
Pernicious anemia	46.7	40.0	13.3

* The figures in the table indicate the percentage distribution.

1.4 was larger in the group with sprue, as was the percentage of patients with a mean corpuscular volume over 130 cubic microns. Finally, an icterus index [31] above the normal value of 6 units was found almost as often in the patients with sprue as in those suffering from pernicious anemia. Values for the icterus index over 10 units were actually found in a greater percentage of the patients with sprue. It is thus difficult to discover in this comparison by identical technics of the morphologic

characteristics of the blood in the two conditions any consistent diagnostic criteria for differentiation of the diseases. The possible differential value of the Arneth count [43] was not studied.

The Bone Marrow.—Mackie and Fairley [47] described the changes in the femoral and tibial bone marrow of a group of patients with sprue who came to autopsy. They observed in different patients instances of hyperplastic marrow such as is found in patients with pernicious anemia, fatty marrow with circumscribed areas of activity and marrow showing gelatinous degeneration. Ashford [48] found both hyperplastic and aplastic histologic pictures in specimens of tibial marrow removed during life. Krjukoff [49] made detailed studies of the marrow obtained for biopsy from the ribs of 16 patients with sprue. He found uniformly a megaloblastic change of the marrow. Since Peabody,[50] in connection with a study of the tibial bone marrow in cases of pernicious anemia, has emphasized the fact that the marrow of a long bone such as the tibia does not necessarily reflect the changes in the marrow of those bones normally containing active cellular marrow in adult life, these discrepancies are easily understood. Our observations, based on biopsy specimens of sternal marrow of 22 patients with sprue and anemia of a macrocytic type, have been reported in detail elsewhere.[51] The specimens obtained showed that in untreated patients with severe anemia the essential change is a proliferation of megaloblasts with suppression of maturation beyond this stage. During remissions induced with liver therapy the marrow tends to return to normal through a transitional stage in which are seen large numbers of normoblasts. Phagocytosed erythrocytes were observed in the specimens of marrow removed at autopsy but not in those removed during life. The cellular changes in the normally active marrow in different stages of the disease were thus similar to those observed in cases of pernicious anemia by Peabody.[50] Judging from the results of others it is probable, however, that hyperplastic marrow in the long bones is not so regularly found or so extensive as in cases of pernicious anemia. A summary of the histologic observations on bone marrow, including changes with therapy, is shown in table 3.

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48. Ashford, B. K.: The Differential Diagnosis of Sprue and Pernicious Anemia, Am. J. Trop. Med. **12**:199 (May) 1932.

49. Krjukoff, A.: Anämie bei Sprue, Folia haemat. **35**:329 (Jan.) 1928.

50. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, Am. J. Path. **3**:179 (May) 1927.

51. Rhoads, C. P., and Castle, W. B.: The Pathology of the Bone Marrow in Sprue Anemia, Am. J. Path. **9**:813, 1933.

TABLE 3.—*Blood Picture and Observations on the Bone Marrow in Patients with Anemia of Sprue* *

Case	Blood Picture: Red Blood Cells, Millions	Hemoglobin, per Cent	White Blood Cells, Thousands	Mean Corpuscular Volume: Reticulocytes, per Cent	Mean Corpuscular Volume: Cubic Microns	Icterus Index	Color Index	Bone Marrow: Biopsy or Autopsy	Source of Bone Marrow	General Cellularity	Megaloblasts and Erythroblasts	Normoblasts	Fat	Comment
Untreated Patients														
9	2.15	54	8.1	1.8	130	2	1.25	Biopsy	Sternum	++	++	++	++	Early though definite megaloblastic preponderance
15	1.76	49	6.2	1.4	126	5	1.39	Biopsy	Sternum	+++	+++	+	+	Moderate megaloblastic proliferation and preponderance
30	1.41	40	3.3	3.2	126	4	1.42	Biopsy	Sternum	++++	++++	—	—	Intense megaloblastic proliferation and preponderance
31	1.42	48	2.2	6.6	140	40	1.69	Biopsy	Sternum	++++	++++	—	—	
32	0.98	28	2.2	0.8	143	25	1.43	Biopsy	Sternum	++++	++++	—	—	
34	2.51	55	3.3	4.8	101	2	1.10	Biopsy	Sternum	++++	++++	—	—	
36	1.96	46	9.8	1.4	114	2	1.17	Biopsy	Sternum	++++	++++	—	—	
37	1.92	42	4.8	2.0	102	5	1.10	Biopsy	Sternum	++++	++++	—	—	
39	2.67	66	7.4	2.2	119	3	1.24	Biopsy	Sternum	++++	++++	—	—	
53	1.15	34	5.1	3.8	131	30	1.48	Biopsy	Sternum	++++	++++	—	—	
58	2.52	63	8.1	3.2	128	3	1.25	Biopsy	Sternum	++++	++++	—	—	
60	3.12	73	7.5	1.6	107	2	1.14	Biopsy	Sternum	++++	++++	—	—	
64	1.25	29	1.8	1.0	104	18	1.16	Biopsy	Sternum	++++	++++	—	—	
68	1.68	55	5.0	4.6	134	5	1.63	Biopsy	Sternum	++++	++++	—	—	
86	2.40	54	1.9	0.4	113	40	1.12	Biopsy	Sternum	++++	++++	—	—	
79	1.46	40	3.0	0.1	121	5	1.37	Biopsy	Sternum	+++	++	+	+	Moderate megaloblastic proliferation and preponderance
76	1.05	29	2.9	8.8	157	12	1.38	Post-mortem	Sternum and femur	++++	++++	—	—	Phagocytosis of red blood cells present
77	2.86	68	7.6	1.6	119	3	1.19	Post-mortem	Sternum and femur	++++	++++	—	—	Sternal marrow red, femoral marrow partly red; lung abscess; microscopically, very loose structure
81	0.97	19	7.3	4.5	103	30	0.98	Post-mortem	Sternum and femur	++++	++++	—	—	Brick-red marrow in sternum and upper third of femur; transfusion; microscopic structure confused; phagocytosed red blood cells
Treated Patients														
51	0.94	19	3.6	4.4	115	10	1.00	1st biopsy	Sternum	++++	++++	+	—	Before remission: many megaloblasts, few normoblasts, almost no fat cells
51	2.97	60	3.3	4.2	100	2	1.01	2d biopsy	Sternum	++	+	+++	++	20 days after intramuscular injection of liver extract; normoblasts predominant
82	0.83	26	3.0	14.0	162	3	1.57	Biopsy	Sternum	++	++	+	+	9th day of oral administration of liver extract; during reticulocyte rise; megaloblasts separating into clumps; normoblasts appearing
75	1.40	29	2.3	21.6	114	6	1.04	1st biopsy	Sternum	+++	++	++	+	9 days after intramuscular injection of liver extract; during reticulocyte rise; decrease in megaloblasts; increase in normoblasts
75	2.69	55	2.8	2.0	99	2	1.02	2d biopsy	Sternum	+	+	++++	+++	30 days after administration of liver extract; late remission; picture in marrow approaches normal except for increased normoblasts

* This table is the same, with modifications, as that used in an earlier article by two of us (Minnich and Castle).[1]

PHYSIOLOGIC OBSERVATIONS

Resemblance of Sprue to Pellagra and Pernicious Anemia.—In each of the diseases, pernicious anemia, pellagra and sprue, disturbances of the gastro-intestinal tract, of the formation of blood and of the central nervous system are associated.[52] In general, in each disease, however, the incidence and degree of disturbance of the three systems of the body differ; and in different persons with each disease the extent of the involvement of any of the three systems is variable. Thus, in over half the cases of pernicious anemia glossitis and digestive disturbances occur, in cases of pellagra these symptoms are probably more constant, and in cases of sprue the diagnosis is almost impossible in their absence. In all three diseases the symptoms and signs relative to the tongue are similar, although in pellagra and in sprue the disturbance is more marked. In all three diseases anemia of the macrocytic type may occur, although it is not so common or so severe in pellagra as in the other two. In none of these conditions is macrocytic anemia invariable, and the development of hypochromic anemia has been reported in each.[53] In many cases of pernicious anemia definite evidence of disturbance of the central nervous system is present. In cases of pellagra mental symptoms, which are sometimes observed in association with pernicious anemia, are more common than is evidence of subacute combined degeneration of the spinal cord. The mental symptoms of sprue, though frequent, are usually not so pronounced as those of pellagra but are perhaps more marked than those of pernicious anemia. Neurologic involvement is by no means as common in sprue as in pernicious anemia or pellagra, but its occasional occurrence has not escaped the notice of some observers and was suggested by the symptoms and signs presented by 8 of our 92 patients.

Many of these comparisons have been made by others. The similarities of the blood picture in pernicious anemia and in sprue have been pointed out by Elders,[54] Wood,[13b] Baumgartner,[37b] Ashford,[28] Fairley,[42] Manson-Bahr [36] and others.[55] The similarities of the gastro-intestinal

52. (*a*) Krjukoff, A.: Die Differentialdiagnose von Addison-Biermerscher Anämie, Sprue und Pellagra, Folia haemat. **45**:188 (Sept.) 1931. (*b*) Rhoads, C. P., and Miller, D. K.: The Production in Dogs of Chronic Black Tongue with Anemia, J. Exper. Med. **58**:585 (Nov.) 1933. Minot and Murphy.[26]

53. Faber, Knud, and Gram, H. C.: Relations Between Gastric Achylia and Simple and Pernicious Anemia, Arch. Int. Med. **34**:658 (Nov.) 1924. Krjukoff, A.: Blut und Blutbildung bei schweren Fällen von Pellagra, Folia haemat. **45**:196 (Sept.) 1931. Ashford.[28]

54. Elders, C.: Tropical Sprue and Pernicious Anaemia: Aetiology and Treatment, Lancet **1**:75 (Jan. 10) 1925.

55. Christian, H. A.: The Achlorhydria Family Tree of Diseases, Northwest Med. **24**:531 (Nov.) 1925. Musser.[40]

disturbance in pellagra and in sprue have been remarked by Wood [13b] and Krjukoff.[52a] Neurologic signs [37] and degenerative changes [38] in the spinal cord in sprue resembling those in pernicious anemia and pellagra have been noted. The cutaneous lesions of pellagra thus remain the outstanding differentiating feature of this disease. It is interesting, however, that pigmentary changes of the exposed surfaces of the body have been noted both in sprue [56] and in pernicious anemia.[57]

For each of these three conditions there has been developed a method of treatment based on a dietary regimen including milk and meat. Before the discovery of liver therapy for pernicious anemia the success of the regimen was distinctly greater in sprue and in pellagra than in pernicious anemia, in which, at best, treatment with a diet high in protein could be described as a palliative measure. In certain instances, however, it was somewhat successful [58] in prolonging the life of the patient. In the treatment of sprue, as an adjunct to the diet the use of liver has been of long standing, although its efficacy has been hard to judge. The original observations of Minot and Murphy [26] on liver therapy in pernicious anemia demonstrated an improvement, not only of the anemia, but also of the lingual and gastro-intestinal manifestations and of the symptoms in the spinal cord. Subsequent work by Cohn, Minot and their associates [21] demonstrated the specific effectiveness of certain fractions of liver, thereafter confirmed by many others. The beneficial action of such liver extracts on the disturbances in the alimentary tract [59] and anemia [60] of pellagra and on the anemia in certain cases of sprue [61] has since been demonstrated. The improvement of symptoms suggestive of lesions of the cord in a few patients with sprue was observed by us to follow therapy with liver extract administered parenterally, as described later. This therapy also produced prompt improvement of the symptoms of the alimentary tract and of the macrocytic anemia of sprue. Since pellagra and pernicious anemia can almost certainly be regarded as deficiency diseases, these similarities alone are suggestive evidence of the validity of a like supposition in respect to sprue.

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56. Ashford.[28] Manson-Bahr and Willoughby.[36]

57. Minot, G. R.: Diseases of the Blood: Clinical Discussion of the Anemias, in Oxford Medicine, New York, Oxford University Press, 1932, vol. 2, p. 589.

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60. Strauss, M. B., and Castle, W. B.: Unpublished observations.

61. Bloomfield and Wyckoff.[22] Richardson and Klumpp.[23] Ashford.[24]

Analogies between the Mechanisms of Deficiency in Pernicious Anemia and Sprue.—The resemblances between the clinical picture and therapeutic response to orally administered liver extracts of patients with pernicious anemia and those of certain patients with sprue have already been summarized. Recent observations appear to demonstrate the nature of the immediate physiologic defects in pernicious anemia leading to a deficiency of "liver extract" in the body. In view of the relatively considerable knowledge of pernicious anemia and its nature, an attempt was made to discover to what extent the etiologic factors already displayed in this disease were present in sprue. Failure of the formation of blood in persons with addisonian pernicious anemia has been demonstrated [62] to be due in large part to the absence of a specific reaction which in the normal person takes place as a result of the presence in the gastro-intestinal tract of a factor in the food (extrinsic) and a factor in the gastric juice (intrinsic). Wills [63] found that autolyzed yeast and liver extract were about equally effective in the treatment of macrocytic anemia of pregnancy in India. Stimulated partly by the suggestions afforded by this work, Strauss and Castle have recently shown that the food factor involved in pernicious anemia is present in autolyzed yeast [64] and is associated with a number of sources of vitamin B_2 (G).[65] So

62: (*a*) Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, Am. J. M. Sc. **178**:748 (Dec.) 1929. (*b*) Castle, W. B.; Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or With Hypochromic Anemia Having No Free Hydrochloric Acid, and of the Rôle of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, ibid. **182**: 741 (Dec.) 1931. (*c*) Wilkinson, J. F.: Pernicious Anaemia: Preliminary Report on the Results Obtained by Treatment with Certain Preparations of Stomach, Brit. M. J. **1**:236 (Feb. 8) 1930. (*d*) Middleton, W. S., and Stiehm, R. H.: The Influence of Gastric Juice on Erythropoiesis in Pernicious Anemia, Am. J. M. Sc. **180**:809 (Dec.) 1930. (*e*) Helmer, O. M.; Fouts, P. J., and Zerfas, L. G.: The Relationship of the Intrinsic Factor to a Hematopoietic Material in Concentrated Human Gastric Juice, ibid. **188**:184 (Aug.) 1934.

63. Wills, Lucy: Treatment of "Pernicious Anaemia of Pregnancy" and "Tropical Anaemia" with Special Reference to Yeast Extract as a Curative Agent, Brit. M. J. **1**:1059 (June 20) 1931.

64. Strauss, M. B., and Castle, W. B.: The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias: Activation of Yeast Derivatives with Normal Human Gastric Juice, New England J. Med. **207**:55 (July 14) 1932; Lancet **2**:111 (July 16) 1932.

65. (*a*) Castle, W. B.: The Etiology of Pernicious Anemia and Related Macrocytic Anemias, Ann. Int. Med. **7**:2 (July) 1933. (*b*) Singer, Karl: Eiertherapie der perniziösen Anämie, Wien. klin. Wchnschr. **45**:1063 (Aug. 25) 1932.

far, however, the food factor has not been identified with any portion of the vitamin B complex.[66] These principles apply as well to the etiology of macrocytic anemia of pregnancy, according to the studies of Strauss and Castle.[67] In 1931 Castle and Taylor[68] discovered that a preparation of liver suitable for parenteral use could readily be made from an already existing extract of liver (fraction G of Cohn and his co-workers) previously used only for oral administration. Since occasional patients with pernicious anemia showed relatively little response to the oral administration of the usual amounts of fraction G, but responded characteristically to parenteral injections of the same material, the suggestion was made that difficulty in the absorption of blood-forming substances from the intestinal tract was involved in these particular patients.[62b] As a result of these observations it appeared reasonable to suppose that at least three mechanisms might be involved in the etiology of pernicious anemia or of the macrocytic anemia of patients responding characteristically to certain liver extracts. First, the food factor might be deficient; second, the gastric factor might be lacking or, third, the normal degree of intestinal absorption might be decreased. It is also clear that different combinations of these defects could produce the same end-result. The possible influence of these etiologic mechanisms in the production of sprue was accordingly investigated.

Observations on Patients with Incomplete Sprue.—In order to eliminate the secondary influence of the diarrhea and other chronic manifestations of the disease, it was considered of paramount importance to discover the factors operative at the onset of the disorder. For this reason patients were selected who were considered to have incomplete sprue, or the "syndrome of nutritional unbalance preceding sprue" of Ashford.[69] Because the degree of anemia of many of these patients

66. Wills, Lucy, and Naish, Alice: A Case of Pernicious Anaemia Treated with Vitamin B_2 from Egg White, Lancet **1**:1286 (June 17) 1933. Wills, Lucy: The Nature of the Haemopoietic Factor in Marmite, ibid. **1**:1283 (June 17) 1933. Diehl, F., and Kühnau, J.: Ist Vitamin B_2 der therapeutisch wirksame äussere Faktor beim Morbus Biermer? Deutsches Arch. f. klin. Med. **176**:149 (Dec.) 1933. Miller, D. K., and Rhoads, C. P.: The Presence in Egg-White and in a Rice-Polishings Concentrate Low in Vitamin B_2 (G) of an Anti-Pernicious Anemia Principle, New England J. Med. **211**:921 (Nov. 15) 1934.

67. Strauss, M. B., and Castle, W. B.: Studies of Anemia in Pregnancy: III. The Etiologic Relationship of Gastric Secretory Defects and Dietary Deficiency to the Hypochromic and Macrocytic (Pernicious) Anemias of Pregnancy and the Treatment of These Conditions, Am. J. M. Sc. **185**:539 (April) 1933.

68. Castle, W. B., and Taylor, F. H. L.: Intravenous Use of Extract of Liver: Maximal Responses of Reticulocytes from a Single Injection Derived from One Hundred Grams of Liver: Preliminary Communication, J. A. M. A. **96**:1198 (April 11) 1931.

69. Ashford.[15, 28]

was slight, studies of the hematopoietic effects of various procedures were impossible. A solution of the difficulty was offered, however, by the suggestion of Rhoads that the tongue be used as an index of therapeutic effects. Although observers in Puerto Rico, among them Ashford [24] and Suárez,[25b] seem not to have commented on the effect of liver extracts or of stomach preparations [70] on the lingual symptoms of sprue, the observations of Minot and Murphy,[26] Middleton and his associates [71] and others on pernicious anemia have demonstrated the coincidence of lingual and hematologic improvement in that disease. Several years ago Manson [85] suggested a study of the tongue in cases of sprue because it reflected the changes in the intestinal tract. The propriety of adopting improvement in the appearance of this organ as an index of improvement of sprue was soon made clear by observations on severely anemic patients. Decrease of the symptoms and signs referable to the tongue invariably and promptly followed the injection of hematopoietically effective doses of liver extract. Observations were therefore next made on the effects of the liver extract on the lingual and gastro-intestinal phenomena of 11 patients with either early sprue or sprue with only moderate anemia. The patients either were maintained on the basal diet in the hospital or were allowed to continue their usual diet at home. In cases 1, 7, 11, 18, 25, 41, 50 and 69 the intramuscular injection of the amount of liver extract derived from 10 Gm. of liver daily or that derived from 100 Gm. of liver weekly completely relieved the symptoms referable to the tongue within from three to five days after the first injection. By the end of a week redness was gone and the reappearance of papillae in denuded areas of the tongue was observed. In the patients having diarrhea the frequency of the stools decreased, and within two weeks most of the stools were formed. The results of the observations in cases 11 and 18 are shown diagrammatically in chart 1. In two other patients (cases 52 and 63) the daily oral administration of liver extract derived from 300 Gm. of liver had a similar effect on the tongue. It thus appeared proper to regard improvement of the tongue in early sprue as a qualitative index of effective therapy comparable to the hematopoietic responses of the anemic patients.

70. Ashford, B. K., and Pons, J. A.: A Clinical Investigation of Thirteen Cases of Anemia of Pernicious Type in Porto Rico, Porto Rico J. Pub. Health & Trop. Med. **7**:167 (Dec.) 1931.

71. Oatway, W. H., Jr., and Middleton, W. S.: Correlation of Lingual Changes with Other Clinical Data, Arch. Int. Med. **49**:860 (May) 1932. Hutter, A. M.; Middleton, W. S., and Steenbock, Harry: Vitamin B Deficiency and the Atrophic Tongue, J. A. M. A. **101**:1305 (Oct. 21) 1933.

Castle and Strauss [72] had observed that the lingual and gastrointestinal symptoms of pernicious anemia were relieved by such combinations of the extrinsic factor and the gastric juice of normal persons as resulted in hematopoietic effects. Various sources of the extrinsic factor, such as beef muscle,[73] eggs,[64b] autolyzed yeast,[63] rice polishings,

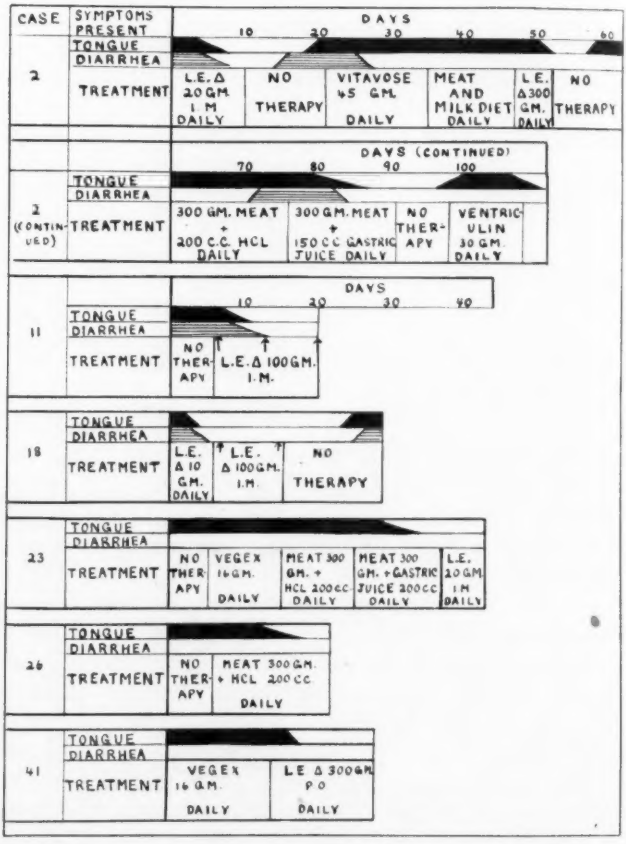

Chart 1.—The effect of liver extract and of sources of the extrinsic factor administered alone or with gastric juice on the lingual and intestinal manifestations of sprue in the early stages or sprue with little anemia. Note that whereas liver extract always relieved the lingual symptoms, beef muscle was not effective in cases 2 and 23 until supplemented with normal human gastric juice. In this and the following charts the phrase L.E. Δ 100 Gm. means liver extract derived from 100 Gm. of liver.

72. Castle.[62a] Strauss and Castle.[60]
73. Castle.[62a] Castle, Heath and Strauss.[62b]

and wheat germ,[64a] were shown to become hematopoietically active when administered with normal human gastric juice to suitable patients with pernicious anemia. Accordingly, certain of these substances in amounts known to be effective in the treatment of pernicious anemia only after contact with normal human gastric juice were administered to patients with incomplete sprue with and without the addition of normal human gastric juice. In chart 1 are shown diagrammatically the results of these observations. Patient 26, after a preliminary control period of six days, was given daily 300 Gm. of beef muscle and 200 cc. of tenth-normal hydrochloric acid. After about six days of this treatment the tongue began to improve and within two weeks clearly showed a reappearance of many of its papillae. In case 41, on the other hand, the daily administration of 16 Gm. of Vegex (a commercial preparation of autolyzed yeast) for fourteen days was without effect. Within two days after the subsequent daily oral administration of liver extract the glossitis began to improve, and within five days the tongue had no longer the signs of an inflammatory process. The explanation of these differences in the effectiveness in sprue of sources of extrinsic factor known to be potent in pernicious anemia only after contact with normal gastric juice was made clear by the following observations:

After a preliminary control period of five days, patient 23 received daily for ten days 16 Gm. of Vegex and during the succeeding period of ten days 300 Gm. of beef muscle and 200 cc. of tenth-normal hydrochloric acid. No effect on the severe glossitis of this patient was observed with either type of extrinsic factor. The dose of 200 cc. of hydrochloric acid was then replaced by 200 cc. of normal human gastric juice, while the administration of the beef muscle was continued as before. Three days later the lingual symptoms were less, and within ten days the tongue appeared entirely normal. Moreover, on the seventh day of the administration of the beef muscle and gastric juice a reticulocyte response of 4 per cent was obtained when the red blood cells numbered 1,400,000 per cubic millimeter. Liver extract derived from 20 Gm. of liver injected daily then caused a second reticulocyte peak of only 8.6 per cent. The tongue remained normal.

In case 2 a more extended series of observations was carried out, as shown in chart 1. It was demonstrated that the lingual symptoms and signs were not relieved in successive periods of ten days or more by the daily administration of 45 Gm. of Vitavose (an extract of wheat germ), of 300 Gm. of beef muscle and 1,500 cc. of milk, or of 300 Gm. of beef muscle and 200 cc. of tenth-normal hydrochloric acid, respectively. On the other hand, the substitution of 200 cc. of normal human gastric juice for the hydrochloric acid caused the tongue to improve after six days and to be entirely free from "inflammation" by the end of ten days.

TABLE 4.—*Results of the Oral and Parenteral Administration of Liver*

Days	Case 10			Case 15			Case 40			Case 44			Case 53			Case 54		
	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent
First Period: Daily Oral Administration of Liver Extract Derived from 300 Gm. of Liver and from 600 Gm. in Cases 78, 90 and 92																		
0	2.34	59	0.8	1.52	37	0.8	1.45	42	1.0	0.89	22	3.2	1.09	34	1.8	1.13	29	0.8
2	2.52	64	2.6	1.66	**41**	**0.4**	1.73	41	1.6	0.81	23	3.2	0.95	30	2.4	0.89	24	0.6
4	2.64	66	1.4	1.51	38	0.8	1.50	38	1.6	0.76	23	4.8	0.91	30	6.4	1.01	28	0.6
6	2.59	63	5.4	1.67	44	5.8	1.73	40	2.2	0.79	24	6.4	0.94	31	17.2	0.89	22	1.6
8	2.69	62	**8.4**	1.63	41	**7.2**	1.70	44	2.6	0.77	25	**9.2**	1.16	30	**35.8**	0.76	21	1.6
10	2.62	68	5.4	2.00	44	4.8	1.76	46	2.2	0.91	27	8.0	1.24	33	30.2	0.80	22	**8.4**
12				1.90	45	2.8							1.46	42	15.6			
14	....	..	...				....	..	...	....	..	...	1.52	44	10.6	....	..	...
16	....	..	...	....	..	...	....	..	...	....	..	...				....	..	...
18	....	..	...	....	..	...	....	..	...	....	..	...	1.89	56	3.6	....	..	...
20	....	..	...	....	..	...	....	..	...	....	..	...	1.91	55	0.2	....	..	...
22	....	..	...	1.90	45	2.0	....	..	...	....	..	...	....	..	...	....	..	...
24	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
26	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
28	....	..	...	1.72	49	1.8	....	..	...	....	..	...	2.05	53	...	....	..	...
5 weeks	....	..	...	2.14	50	1.0	....	..	...	....	..	...	3.45	78	1.2	....	..	...
6 weeks	....	..	...	2.12	54	1.0	....	..	...	....	..	...				....	..	...
7 weeks	....	..	...	2.16	54	0.8	....	..	...	....	..	...	....	..	...	....	..	...
Second Period: Daily* Parenteral Administration of Liver Extract in Amounts Indicated																		
	L. E. △ 10 i.m.†			L. E. △ 10 i.m.			L. E. △ 10 i.m.			L. E. △ 10 i.m.			No Therapy			L. E. △ 10 i.m.		
0	2.62	68	5.4	2.16	54	0.8	1.76	46	2.2	0.91	27	8.0	....	..	...	0.80	22	8.4
2	2.74	69	2.2	1.97	48	1.6	1.52	45	3.0	0.97	25	5.8	....	..	...	0.86	22	16.0
4	2.70	68	4.6	2.24	58	0.8	1.83	48	8.0	0.94	27	6.2	....	..	...	1.42	32	**25.4**
6	2.66	67	2.0	2.38	63	0.6	2.32	51	**15.0**	0.99	28	23.0	....	..	...	1.83	38	15.0
8	3.12	72	2.4	2.56	60	1.0	....	..	...	1.19	34	**28.0**	....	..	...	1.81	42	9.2
10	2.95	68	2.2	2.30	62	2.0	....	..	...	1.35	34	15.2	....	..	...	1.73	46	5.0
12	2.87	72	2.4	L. E. △ 50 i.v.			2.95	58	1.8	1.59	38	4.0	....	..	...	2.00	46	4.0
14	2.72	68	3.4	2.74	65	1.0	....	..	...	1.93	40	4.8	....	..	...	2.18	50	5.0
16	2.72	72	1.4	**2.63**	**58**	1.0	....	..	...	2.37	42	3.6	....	..	...	2.27	55	3.6
18	3.03	74	6.0	2.79	**65**	0.8	....	..	...	2.68	45	3.0	....	..	...	2.08	48	9.0
20							....	..	...	2.80	55	2.8	....	..	...	2.17	55	2.2
22	....	..	...	....	..	...	3.46	69	0.6	2.98	58	1.0	....	..	...	2.36	56	1.4
24	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	2.41	57	1.6
26	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	2.62	54	2.2
28	....	..	...	....	..	...	....	..	...	3.05	59	1.4	....	..	...	2.75	55	2.2
5 weeks	....	..	...	....	..	...	4.05	76	...	....	..	...	....	..	...	2.48	58	1.2
																Ferric Ammonium Citrate, 6 Gm.		
6 weeks	....	..	...	....	..	...	....	..	...	3.58	65	0.1	....	..	...	2.65	60	**3.0**
7 weeks	....	..	...	....	..	..	....	..	...	3.98	75	1.2	....	..	...	2.50	61	0.8
8 weeks	....	..	...	....	..	..	....	..	...				....	..	...			
9 weeks	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
10 weeks	....	..	...	....	.	...	....	..	...	....	..	...	....	..	...	....	..	...
11 weeks	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
12 weeks	....	..	...	....	..	..	....	..	...	....	..	...	....	..	...	....	..	...

* Exceptions should be noted in cases 90 and 92.
† △ 10 indicates: derived from 10 Gm. of liver.

Case 55			Case 68			Case 78			Case 82			Case 83			Case 90			Case 92		
Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent
First Period: Daily Oral Administration of Liver Extract Derived from 300 Gm. of Liver and from 600 Gm. in Cases 78, 90 and 92																				
1.17	32	0.6	1.88	58	0.4	1.26	25	1.4	0.81	25	2.2	1.02	26	2.6	2.25	52	0.8	1.24	22	1.6
1.09	30	1.0	2.26	65	0.8	0.96	28	1.4	0.86	22	0.4	0.98	27	4.6	2.29	57	2.4	1.13	22	2.4
1.05	28	0.6	1.87	53	1.2	0.88	26	1.4	0.83	22	0.4	0.94	26	4.8	2.12	50	1.8	0.92	21	2.2
1.05	36	2.4	1.94	56	1.6	1.01	31	3.8	0.89	24	1.6	1.09	30	**19.0**	2.41	55	2.8	1.26	23	1.4
1.21	38	6.2	2.10	59	1.8	1.40	33	**16.0**	0.84	21	5.4	0.97	30	18.0	2.23	55	1.8	1.32	25	4.6
1.28	37	**8.8**	1.93	55	1.6	1.51	37	8.6	0.83	26	**14.0**	1.11	29	10.2	2.24	57	3.6	1.00	23	2.6
1.74	42	8.6																		
1.78	46	3.0	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
			....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
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....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...

Second Period: Daily* Parenteral Administration of Liver Extract in Amounts Indicated

L. E. △ 10 im.			L. E. △ 10 i.m.			L. E. △ 20 i.m.			L. E. △ 10 i.m.			L. E. △ 10 i.m.			L. E. △ 100 i.v. Every 10 Days			L. E. △ 100 i.v. Every 10 Days		
1.78	46	3.0	1.93	55	1.6	1.51	37	8.6	0.83	26	14.0	1.11	29	10.2	2.24	57	3.6	1.00	23	2.6
1.70	48	2.8	2.35	59	1.0	1.47	46	5.2	0.92	29	8.0	1.34	34	11.2	2.32	60	2.4	1.04	21	2.4
1.63	49	4.4	2.49	62	1.0	1.54	43	2.4	1.03	30	6.0	1.40	36	8.2	2.53	63	2.2	1.36	29	**29.8**
1.35	46	**5.0**	2.78	63	0.8	1.65	45	4.2	1.06	31	8.0	1.60	40	3.4	3.10	69	**6.0**	1.69	32	20.4
1.60	43	3.0	2.63	60	1.8	1.60	44	5.4	1.26	35	4.2	1.69	41	2.8	2.80	67	2.6	1.83	34	10.2
L. E. △ 300 p.o.			2.47	61	1.0	1.95	52	3.4	1.24	38	6.8	L. E. △ 50 Every 4 Da.			3.07	71	2.6	....	..	...
....	..	...	2.83	68	0.8	2.27	52	3.6	1.52	42	3.0	1.40	42	5.6	2.95	68	1.0	2.20	40	...
....	..	...				....	..	...	1.51	42	4.8	....	..	...	3.30	75	1.0	....	..	...
			L. E. △ 50 i.v.																	
....	..	...	2.50	69	1.2	....	..	...	1.43	42	2.8	1.85	46	1.6	3.69	73	1.2	3.03	45	...
2.33	58	2.8	3.09	86	1.0	....	..	...	1.67	44	4.4	....	..	...	3.39	78	1.4	....	..	...
....	..	...	2.54	63	1.0	2.92	62	3.6	1.72	46	4.4	....	..	...	....	..	...	....	..	...
....	..	...	2.95	66	0.6	....	..	...	1.72	50	3.6	....	..	...	....	..	...	3.29	53	...
....	..	...	....	..	...	....	..	...	1.80	46	0.6	2.29	54	2.8	3.39	75	...	....	..	...
2.10	56	1.4	....	..	...	3.17	70	...	1.71	52	2.2	....	..	...				....	..	...
....	..	...	....	..	...	....	..	...	1.84	52	4.0	2.30	57	2.6	....	..	...	3.05	56	...
									L. E. △ 20 i.m.									....	..	...
2.62	66	...	3.31	74	0.8	3.11	68	...	2.50	62	2.8	3.41	64	0.6	....	..	...	3.91	60	...
2.59	63	...	....	..	...	3.76	79	...	2.68	68	1.8	3.00	63	0.4	....	..	...	....	..	...
3.03	64	...	....	..	...	3.80	79	...	2.94	68	2.0	....	..	...	....	..	...	3.78	62	...
3.21	60	...	....	..	...							2.90	65	...	....	..	...	....	..	...
			....	..	...	....	..	...	....	..	...	3.27	67	0.8	....	..	...	....	..	...
....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
....	..	...	....	..	...	....	..	...	....	..	...	3.40	68	...	....	..	...	4.63	73	...
....	..	...	....	..	...	....	..	...	....	..	...	3.74	71	...	....	..	...			

Similarly, the oral administration of 30 Gm. of Ventriculin daily and the oral and intramuscular administration of liver extract each caused improvement of the tongue after the reappearance of "inflammation" during periods when therapy had been discontinued.

The interpretation of these results is clearly suggested by analogous observations in cases of pernicious anemia. The lingual and gastrointestinal symptoms of early sprue are thus apparently dependent on a deficiency mechanism, as already suggested but not delineated by Ashford,[15] Elders [18] and others.[74] Since liver extracts and combinations of the extrinsic and the intrinsic factor known to be capable of promoting the formation of blood in pernicious anemia influence favorably the glossitis of both diseases, the defect of nutrition producing the symptoms in the two diseases is apparently similar. In different patients with sprue, however, the disturbance was apparently brought about by different mechanisms resulting in the same final "liver extract" defect. Thus, in the patient in whom the glossitis was improved by the administration of the extrinsic factor alone (case 26) it is probable that the intrinsic factor was present in the gastric contents. On the other hand, in those patients (cases 2 and 23) in whom no improvement of the glossitis occurred until both the extrinsic and the intrinsic factor were administered it is probable that insufficient intrinsic factor was present to produce benefit without a supplement from a normal person. In its early manifestations sprue is thus clearly dependent on deficiencies closely related to, if not identical with, those already described in association with pernicious anemia.

Observations on Patients with Fully Developed Sprue and Anemia.—In some patients with sprue oral therapy with liver extract or stomach preparations in amounts usually effective in the treatment of pernicious anemia has not produced significant improvement of the blood values.[75] This result has led to the assumption that the conditions producing the macrocytic blood picture in sprue are not always the same,[70] and some type of aplastic anemia has been hypothecated to explain the failure of therapy.[76] In table 4 are shown the hematopoietic results in 13 patients with advanced sprue and severe macrocytic anemia of the daily oral administration for a period of ten or more days of liver extract derived from 300 or 600 Gm. of liver, as indicated. Except in cases 40, 68, 90 and 92, the oral administration of this amount of liver extract provoked a significant increase in reticulocytes. This therapy was immediately followed in 9 cases by the daily intramuscular injection of the same

74. Maclean.[7] Grant.[8]

75. Ashford, B. K.: An Evaluation of Liver Extract in the Treatment of the Anemias of Sprue, J. A. M. A. **91**:242 (July 28) 1928. Ashford and Pons.[70]

76. Suárez.[25b] Fairley, Mackie and Billimoria.[42] Baumgartner.[43]

extract derived from 10 Gm. of liver. In case 78 twice this dosage was employed. In cases 90 and 92 liver extract derived from 100 Gm. of liver was given intramuscularly at ten day intervals. In cases 40, 90 and 92, in which there had not been a reticulocyte response to orally administered liver extract, the intramuscular injection of this material resulted in a significant increase of reticulocytes. In case 68, in which likewise there was no response to oral therapy in the first period, although no reticulocyte response appeared from the daily intravenous administration of the liver extract derived from 50 Gm. of liver, the blood values rose steadily. In cases 44, 54 and 55 the first response to orally administered liver extract was not sufficiently great to prevent a second rise of the reticulocyte count in response to parenteral administration. In cases 10, 15, 78, 82 and 83 there was no second reticulocyte response to the parenteral administration of liver extract, but the blood values were progressively increased. Additional illustrations of the effectiveness of parenterally administered liver extracts will be found in tables 5, 6 and 11. In our experience the response of the lingual and gastro-intestinal symptoms in patients in the advanced stage of sprue was scarcely less striking than in patients in the early stages of the disease, especially when the material was given by parenteral injection. Since the anemia of all these patients was distinctly improved by means of a liver extract effective in pernicious anemia, administered if necessary by injection, the therapeutic failures noted by others with orally administered products do not necessarily indicate a different basis for the failure of production of blood in such cases of sprue. These results clearly suggest factors of deficiency in the advanced stage of the disease similar to those observed in sprue in the early stages and in addisonian pernicious anemia. Accordingly, a study was undertaken of the etiologic relationship of dietary deficiency, changes in gastric secretions and disturbances of intestinal absorption to fully developed sprue and anemia.

(*a*) Etiologic Significance of Deficiency of the Dietary (Extrinsic) Factor: The use of diets containing rare meat has attained some degree of success in the treatment of sprue and the associated anemia.[77] Ashford [75] and Baumgartner and Case [78] have described moderate reticulocyte responses with such a diet without liver. Since beef muscle is an excellent source of the extrinsic factor, the explanation of the hematopoietic effectiveness of these diets in the treatment of sprue is possibly afforded by the facts already discovered in connection with pernicious anemia [73] and by the observations on the tongue in cases of sprue already reported. If the analogies suggested are correct, in those

77. Ashford.[28] Manson-Bahr and Willoughby.[36] Elders.[54]

78. Baumgartner, E. A., and Case, C. E.: Reticulocyte Response in a Case of Tropical Sprue on a Diet Not Including Liver, Clifton M. Bull. **16**:183, 1930.

TABLE 5.—*Results of the Daily Addition to the Basal Diet of 300 Gm. of Beef Muscle and 1,500 Cc. of Milk, and of Subsequent Therapy with Orally and Parenterally Administered Liver Extract Effective in Pernicious Anemia*

Days	Case 5			Case 17			Case 19			Case 22			Case 32			Case 35			Case 37			Case 42			Case 79		
	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent
First Period: Daily Addition of 300 Gm. of Beef Muscle and 1,500 Cc. of Milk to Basal Diet																											
0	1.21	44	1.4	2.56	75	1.2	1.55	36	0.6	1.98	56	0.8	1.23	31	0.8	2.14	50	0.8	1.62	42	0.8	2.18	63	0.8	1.46	40	0.4
2	1.78	45	2.8	2.46	72	1.0	1.23	32	1.0	2.18	53	0.8	1.27	28	0.8	1.75	46	0.6	1.58	44	0.4	2.46	65	1.0	1.38	38	1.0
4	1.56	44	2.2	2.66	81	2.4	1.21	30	2.6	2.47	59	0.8	1.30	29	1.2	1.92	46	1.4	1.53	40	0.4	2.53	65	0.8	1.48	37	1.0
6	1.51	48	1.6	2.68	79	3.6	1.22	32	3.0	2.35	58	0.8	1.10	31	0.4	2.14	50	1.0	1.75	47	0.8	2.31	61	0.8	1.51	39	2.8
8	1.43	44	3.4	2.70	79	4.4	1.19	30	**3.6**	2.17	54	0.6	1.01	29	0.8	1.87	46	1.0	1.88	43	1.4	2.34	66	0.8	1.47	41	**5.0**
10	1.61	54	**3.6**	2.96	77	**4.6**	1.25	32	2.2	2.22	54	0.8	1.25	28	0.6	....	44	1.8	1.85	43	1.8	2.20	64	1.0	1.62	41	3.2
12	1.67	43	6.4	....	..	...	1.24	32	2.0	2.31	55	1.0	1.00	31	1.0	1.78	46	1.2	1.70	42	2.2	2.56	61	4.2			
14	1.51	53	7.0	3.20	78	2.6	1.07	26	1.6	2.24	58	0.8	1.10	27	1.0	1.77	44	1.6	1.92	42	2.0	2.86	62	**6.2**	....	..	...
16	1.58	54	2.6	....	..	...	1.14	26	2.0	1.76	57	2.0				1.55	44	1.8	2.05	50	2.8	2.64	63	1.8	....	..	...
18	1.36	49	3.8	2.88	78	3.4	1.32	27	2.0	2.35	53	2.4	....	..	...	1.90	43	1.6	1.71	49	3.6	1.96	62	1.8	....	..	...
20	1.83	56	1.8	3.37	82	1.8	1.11	29	1.8	2.45	56	2.8	....	..	...	1.85	48	3.0	2.20	51	2.0	2.67	64	1.2	....	..	...
22	1.91	51	1.8	....	..	...	1.14	25	1.6	2.36	57	2.6	....	..	...	1.85	50	2.0				2.60	61	3.8	....	..	...
24	2.33	57	1.4	2.81	73	1.0				2.40	58	1.6	....	..	...	1.65	46	2.0	....	..	...	2.85	64	1.0	....	..	...
26	2.02	57	1.4	2.88	73	2.0	....	..	...	2.70	65	1.4	....	..	...	1.82	46	2.0	....	..	...				....	..	...
28				2.90	70	1.4	....	..	...	2.45	65	1.6	....	..	...	1.64	46	**4.6**	....	..	...	....	..	...	....	..	...
5 weeks	....	..	...				....	..	...	2.54	64	0.6	....	..	...	2.30	52	2.4	....	..	...	....	..	...	....	..	...
6 weeks	....	..	...	....	..	...	....	..	...	2.76	64	0.8	....	..	...	2.49	47	2.4	....	..	...	....	..	...	....	..	...
Second Period: Daily Oral Administration of Liver Extract Derived from 300 Gm. of Liver																											
0	2.02	57	1.4	2.90	70	1.4	1.14	25	1.6	....	..	...	1.04	31	1.8	2.49	47	2.4	1.59	42	1.6	2.85	64	1.0	1.62	41	3.2
2	2.19	61	1.6	2.81	69	1.6	0.96	25	2.0	....	..	...	1.15	31	1.4	2.73	47	1.6	1.56	38	2.0	2.69	60	1.0	1.70	43	2.8
4	2.18	64	0.6	3.10	64	**3.2**	1.06	27	3.4	....	..	...	0.89	33	1.0	2.64	50	1.8	1.78	45	2.4	2.70	63	0.8	1.64	37	1.6
6	2.11	61	0.8	3.20	65	1.0	1.01	26	**4.2**	....	..	...	1.23	31	2.0	2.58	49	2.0	2.09	45	2.0	2.85	60	0.8	1.33	36	1.2
8	1.84	60	0.8	2.96	68	1.4	1.19	29	2.4	....	..	...	1.18	34	2.8	2.51	50	1.6	1.87	47	1.6	2.76	58	5.6	1.25	35	0.4
10	1.76	56	2.4	3.39	69	1.2	1.28	26	1.6	....	..	...	1.51	37	**7.4**	2.65	51	1.0	1.74	47	0.8	2.77	58	**7.8**			
12										....	..	...	1.36	38	4.6							2.55	60	3.0	....	..	...
14	....	..	...	....	..	...	....	..	...	....	..	...	1.48	40	4.0	....	..	...	....	..	...	2.42	58	4.0	....	..	...
3 weeks	....	..	...	....	..	...	....	..	...	....	..	...				....	..	...	....	..	...	2.44	57	3.6	....	..	...
Third Period: Daily Parenteral Administration of Liver Extract Derived from 10 Gm. of Liver																											
0	1.76	56	2.4	3.39	69	1.2	1.28	26	1.6	....	..	...	1.48	40	4.0	2.72	50	2.2	1.74	47	0.8	2.44	57	3.6	1.25	35	0.4
2	1.87	53	1.6	3.27	65	1.4	0.98	22	1.6	....	..	...	1.25	38	1.6	2.56	48	2.2	1.77	46	0.8	2.77	58	3.2	1.70	39	3.8
4	1.55	55	1.8	2.99	61	2.6	1.02	26	4.0	....	..	...	1.47	40	1.0	3.02	49	1.0	1.80	49	0.8	2.79	54	2.8	1.62	40	4.3
6	1.97	58	2.2	3.57	65	1.8	1.08	25	**15.8**	....	..	...	1.50	45	1.4	2.99	49	1.6	1.74	48	1.4	2.57	56	5.0	1.56	40	**9.2**
8	....	..	4.0	3.19	58	1.6	1.50	30	9.2	....	..	...	1.36	40	3.6	3.04	50	1.0	1.97	49	2.8	2.94	59	**7.0**	1.51	42	8.4
10	2.81	61	4.0	3.46	62	2.0	....	..	...	....	..	...	1.65	42	1.2	3.21	51	1.6	1.74	48	**5.9**	3.20	57	4.6	1.55	46	4.8
12	3.00	63	4.2				1.45	26	6.0	....	..	...	1.59	44	1.0	3.12	49	1.4	1.90	50	5.2	2.97	55	3.2	1.51	44	2.6
14	2.60	64	**7.2**	....	..	...	1.92	29	5.0	....	..	...	1.60	44	1.2				2.37	54	4.8	3.28	58	2.6	1.58	44	3.4
16	2.70	69	2.4	....	..	...	1.37	25	6.4	....	..	...	....	..	...	....	..	...	2.50	54	4.2				1.69	47	3.8
18	2.76	72	2.4	....	..	...	1.50	26	4.8	....	..	...	1.96	45	2.0	....	..	...	2.45	61	3.0	....	..	...	1.71	47	5.2
20	2.96	69	4.0	....	..	...				....	..	...				....	..	...	2.67	62	2.2	....	..	...	1.91	52	2.2
22				....	..	...				....	..	...				....	..	...				....	..	...	2.14	59	2.2
24	....	..	...	....	..	...				....	..	...				....	..	...	2.58	64	1.0	....	..	...	1.97	49	3.0
26	....	..	...	....	..	...				....	..	...				....	..	...				....	..	...	1.89	51	3.4
28	....	..	...	....	..	...				....	..	...				....	..	...				....	..	...	2.45	57	5.4

patients with sprue and macrocytic anemia in whom sufficient intrinsic factor is present in the gastric juice (and in whom intestinal absorption is adequate) the administration of beef muscle alone should provoke a reticulocyte response. These conditions were apparently satisfied in 5 of our 9 patients given, in addition to the basal diet, 300 Gm. of meat and 1,500 cc. of milk daily. In cases 5, 17, 19, 42 and 79 there was attained a significant increase in the reticulocyte count which became maximal by the end of fourteen days of such therapy (table 5). In cases 22, 35 and 37 a delayed reticulocyte response of doubtful significance occurred, but a gradual increase in red blood cells took place. In case 32 no evidence of increased hematopoietic activity appeared. In 4 of these 9 patients (cases 17, 19, 32 and 42) the subsequent daily oral administration of liver extract derived from 300 Gm. of liver produced a second rise in the reticulocyte count (table 5). Subsequent daily parenteral administration of liver extract derived from 10 Gm. of liver produced a reticulocyte response in cases 5, 19, 37, 42 and 79.

Another active source of the extrinsic factor in pernicious anemia is autolyzed yeast.[64] Observations were accordingly made under controlled conditions on the effects of two preparations of autolyzed yeast on 9 patients with sprue and severe anemia. Dried brewers' yeast was mixed with a small amount of water and placed in the incubator for periods of from ten to fourteen days or until the material had turned brown and had a characteristic odor. This preparation of autolyzed yeast was given daily to 6 patients in amounts indicated in terms of the original weight of dried yeast (table 6). Four of these patients (cases 2, 9, 31 and 68) showed a reticulocyte response; the 2 remaining patients (cases 15 and 40) did not. In case 15 there was subsequently a response to orally administered liver extract with a significant rise in reticulocytes; there was none in case 40. In case 40 in response to the subsequent parenteral administration of liver extract a significant increase in reticulocytes appeared. A commercial preparation of autolyzed yeast, Vegex, was administered in daily doses of 12 or 16 Gm., as indicated in table 6, during the first periods of observation on another patient (case 86). A questionable reticulocyte response appeared. In 2 other patients (cases 49 and 72) liver extract derived from 300 Gm. of liver was given daily during the first period of observation and resulted in a significant reticulocyte response. In each patient in the second period larger reticulocyte responses were obtained from the daily administration of 12 Gm. of Vegex. It is thus clear that in cases 49 and 72 the effect of 12 Gm. of Vegex was greater than the effect of liver extract derived from 300 Gm. of liver.

In summarizing the results obtained from the administration to 18 patients of sources of the extrinsic factor consisting of either beef

TABLE 6.—*Results of the Oral Administration of Preparations of Autolyzed Yeast and of Oral and Parenteral Administration of Liver Extract*

Days	Autolyzed Yeast, 60 Gm. Case 2			Autolyzed Yeast, 120 Gm. Case 9			Autolyzed Yeast, 180 Gm. Case 15			Autolyzed Yeast, 120 Gm. Case 31			Autolyzed Yeast, 180 Gm. Case 40			Autolyzed Yeast, 120 Gm. Case 68			Vegex, 16 Gm. Case 86			L. E. △ 300 Case 49			L. E. △ 300 Case 72		
	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloeytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloeytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloeytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloeytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloeytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloeytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloeytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloeytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloeytes, per Cent
First Period: Daily Oral Administration of Various Substances as Indicated																											
0	1.56	32	3.4	1.98	53	1.2	2.06	50	1.0	1.28	49	4.0	1.38	45	2.0	1.32	47	3.6	1.50	50	3.4	0.57	18	1.0	0.87	22	1.2
2	1.85	33	1.8	2.00	51	0.8	1.80	53	1.2	1.50	45	3.0	1.23	42	1.6	1.44	47	2.4	2.00	52	1.6	0.62	16	1.4	0.92	22	1.0
4	1.73	34	2.8	2.48	58	2.6	1.73	47	0.8	1.42	48	**6.6**	1.45	45	1.0	1.83	53	1.2	2.15	55	1.8	0.85	18	5.0	0.98	20	1.8
6	1.45	35	7.8	2.12	56	4.0	1.56	43	0.8	1.32	42	4.0	1.45	46	1.6	1.55	50	1.2	1.76	51	2.4	0.58	18	5.8	0.78	18	7.4
8	1.69	38	8.4	2.25	55	6.8	1.69	46	0.8	1.43	45	2.8	1.25	42	0.8	1.68	55	**4.6**	1.91	57	2.6	0.60	18	**6.6**	0.98	25	16.0
10	1.72	35	**12.8**	2.42	60	**8.2**	1.79	45	0.8	1.26	41	2.6	1.45	42	1.0	1.70	50	3.0	2.22	55	3.6	0.76	17	3.0	1.25	31	**16.4**
12	1.81	38	4.6	2.39	56	5.4				1.42	41	2.2							2.15	52	**3.8**						
14	2.01	38	3.6	2.36	57	2.4	....	..	...				....	..	...	....	..	...	1.99	55	2.0	....	..	...	....	..	...
16	1.77	36	4.8	2.15	54	1.8	....	..	...	....	..	...	....	..	...	....	..	...				....	..	...	....	..	...
18	1.98	37	3.8	2.37	62	2.0	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
20	2.10	38	3.4	2.59	66	2.4	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
22				2.71	74	1.8	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
24	....	..	...	2.51	67	3.0	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
26	....	..	...	2.50	59	1.2	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
28	....	..	...	2.23	56	4.4	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
Second Period: Daily Oral Administration of Various Substances as Indicated																											
	L. E. △ 300			L. E. △ 300			L. E. △ 300			L. E. △ 300			L. E. △300			L. E. △ 300			No Therapy			Vegex, 12 Gm.			Vegex, 12 Gm.		
0	2.10	38	3.4	2.23	56	4.4	1.52	37	0.8	1.42	41	2.2	1.45	42	1.0	1.88	58	1.4	1.99	55	2.0	0.76	17	3.0	1.25	31	16.4
2	2.00	39	3.8	2.12	51	4.2	1.66	41	0.4	1.42	42	2.6	1.73	41	1.6	2.26	65	0.8	2.18	57	2.2	0.70	21	4.8	1.57	38	10.8
4	2.19	39	4.6	1.98	54	1.8	1.51	38	0.8	1.24	37	3.4	1.50	38	1.6	1.87	53	1.2	2.34	55	1.2	0.80	19	3.0	1.78	38	13.4
6	1.92	46	**5.4**	2.01	51	1.2	1.67	44	5.8	1.38	39	3.2	1.73	40	2.2	1.94	56	1.6	1.83	52	1.0	0.70	18	5.6	2.01	40	**17.4**
8	1.79	41	3.0	1.66	46	2.0	1.63	41	**7.2**	1.10	34	**5.8**	1.70	44	1.8	2.10	59	1.8	2.02	52	1.4	0.74	20	9.8	2.35	45	8.6
10	2.49	40	3.6	2.04	50	2.2	2.00	44	4.8	1.25	40	5.7	1.76	46	2.2	1.93	55	1.6	1.88	50	1.2	0.81	22	**14.6**	1.90	53	5.4
12				2.21	53	1.0	1.59	45	2.8	1.32	43	3.8							2.11	58	2.2	1.00	27	12.8	**1.46**	51	5.8
14	....	..	...				....	..	...				....	..	...	....	..	...	2.21	53	1.2	1.24	30	6.4			
16	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	2.17	51	1.8	1.05	28	6.0	....	..	...
18	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	1.89	48	1.0	1.18	25	5.2	....	..	...
20	....	..	...	....	..	...	1.90	45	2.0	....	..	...	....	..	...	....	..	...	2.04	51	0.8				....	..	...
22	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	1.88	47	0.8	....	..	...	....	..	...
24	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	1.87	50	1.0	....	..	...	....	..	...
26	....	..	...	....	..	...	1.72	49	1.8	....	..	...	....	..	...	....	..	...	1.77	50	3.6	....	..	...	....	..	...
28	....	..	...	....	..	...	(table 4)			....	..	...	....	..	...	....	..	...	1.76	41	2.0	....	..	...	....	..	...
Third Period: Daily Parenteral Administration of Liver Extract Derived from 10 Gm. of Liver																											
0	2.49	40	3.6	2.21	53	1.0	2.16	54	0.8	1.21	46	3.4	1.76	46	2.2	1.93	55	1.6	1.76	41	2.0	1.18	25	5.2	1.46	51	5.8
2	2.34	40	3.2	1.67	48	1.4	1.97	48	1.6	1.28	41	2.6	1.52	45	3.0	2.35	59	1.0	1.60	40	1.8	1.09	30	5.4	2.36	54	3.8
4	2.11	38	1.4	2.17	48	1.2	2.24	58	0.8	1.28	35	2.2	1.83	48	8.0	2.49	62	1.0	1.59	38	**1.0**	1.15	29	4.6	2.51	55	3.2
6	2.59	44	3.8	2.27	50	2.6	2.38	63	0.6	1.37	44	1.6	2.32	51	**15.0**	2.78	63	0.8	1.56	38	3.0	1.02	32	5.6	2.59	54	1.8
8	2.63	41	1.6	2.23	47	1.6	2.56	60	1.0	1.37	41	1.6	....	..	...	2.63	60	1.8	1.63	44	10.6	1.21	32	**7.2**	2.55	55	1.0
10	2.59	38	1.6	2.38	53	2.0	2.30	62	2.0	1.32	44	6.8	....	..	...	2.47	61	1.0	1.71	52	**12.6**	1.30	34	6.2	2.84	57	1.0
12	(table 10)			L. E. △ 50 i. m.			L. E. △ 50 i. v.			1.66	47	**9.8**	2.95	58	1.8	2.83	68	0.8	1.90	45	9.6	1.44	36	5.4	3.17	60	1.0
14	....	..	...	2.40	45	1.4	2.74	65	1.0	1.83	51	6.6	....	..	...	L. E. △ 50 i. v.			2.36	50	7.4	1.37	36	7.2	....	..	...
16	....	..	...	2.23	40	3.2	2.63	58	1.0	L. E. △ 50 i. v.			....	..	...	2.50	69	1.2	2.31	52	6.8	1.47	41	6.0	....	..	...
18	....	..	...	2.33	48	**3.6**	2.79	65	0.8	2.12	53	3.6	....	..	...	3.09	66	1.0	2.34	53	2.8	1.58	36	5.2	....	..	...
20	....	..	...	(table 10)						2.55	56	2.6	....	..	...	2.54	63	1.0	2.50	56	1.8				3.20	67	1.0
22	....	..	...	....	..	...	....	..	...	2.65	57	2.8	3.46	69	0.6	2.95	66	0.6	2.72	57	3.6	....	..	...	....	..	...
24	....	..	...	....	..	...	....	..	...	2.63	55	1.6	....	..	...	....	..	...	3.17	60	2.8	....	..	...	....	..	...
26	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...
28	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	3.37	67	...
5 weeks	....	..	...	....	..	...	....	..	...	....	..	...	4.05	76	...	3.31	74	0.8	....	..	...	....	..	...	3.36	70	...

muscle or preparations of autolyzed yeast, case 40 must be excluded. In this case there was no reticulocyte response to any material, including liver extract, when orally administered. Since the subsequent reticulocyte response to parenterally administered liver extract was definite, some degree of intestinal impermeability probably rendered the patient unsuitable for the trial of orally administered material. In 11 of the remaining 17 patients there was a significant reticulocyte response which attained a peak on or before the fourteenth day of therapy. Three patients (cases 22, 35 and 37) showed a gradual increase in the blood values without a definite reticulocyte response at the expected time. In case 86 no trial of orally administered liver extract followed the doubtful response to Vegex. In case 22 no subsequent determination of the response of the patient to orally administered liver extract was made. In the 2 remaining cases (15 and 32) there was no reticulocyte response to sources of the extrinsic factor, but there was a subsequent response to orally administered liver extract in a dosage not as effective in cases 49 and 72 as the daily oral administration of 12 Gm. of Vegex. In cases 15 and 32 it was therefore impossible to detect the presence of the intrinsic factor by the administration of material containing the extrinsic factor. In 3 patients (cases 22, 35 and 37) a minimal amount of intrinsic factor was probably present but distinctly less than in the 11 patients who responded to the administration of the extrinsic factor with a rise in reticulocytes. Thus, the ability to react favorably to sources of the extrinsic factor, whether judged by the reticulocyte response or by the improvement of the tongue, is a variable condition in different patients with sprue. It is therefore logical to examine the possibility that many cases of sprue are produced by deficiency of the diet. Herein the situation in sprue apparently differs from that in pernicious anemia in that a defect of the intrinsic factor of the stomach is almost invariably found in patients with classic addisonian pernicious anemia in relapse.[73] On the contrary, in treated patients with pernicious anemia Barnett [79] has apparently observed the presence of the intrinsic factor, which under these circumstances has also been observed to reappear when previously absent.[62b] Incidentally, because of the fact that sources of the extrinsic factor without added gastric juice were found to be hematopoietically effective in certain patients with sprue, grave doubt is thrown on the inferences of Morris and his co-workers [80] who alleged that the defect in pernicious anemia does not involve a

79. Barnett, C. W.: The Significance of the Gastric Secretions in Pernicious Anemia, Am. J. M. Sc. **182**:170 (Aug.) 1931.

80. Morris, R. S.; Schiff, Leon; Burger, George, and Sherman, J. E.: A Specific Hematopoietic Hormone in Normal Gastric Juice, J. A. M. A. **98**:1080 (March 26) 1932.

reaction with an extrinsic factor but depends solely on a defect of the gastric secretion.

Accordingly, an investigation was made of the individual diets of 63 of the 92 patients selected entirely at random. Particular attention was paid to the character of the diet for years before the onset of the disease. The method of taking the dietary histories included questioning the patient as to his particular likes and dislikes in food and as to whether his diet differed in any way from that of other members of his family. He was asked to describe an average daily menu. In addition, he was questioned as to the number of times per day, week or month that he ate specific foods common in the Puerto Rican diet. Although the taking of a dietary history is admittedly a difficult procedure in which the quality of the patient's answers may be as important as his quantitative statements in indicating the amount and type of food taken, the monotony of the fare of the Puerto Rican peasants aided the investigation by limiting the possibilities.

In table 7 an attempt has been made to present in a roughly quantitative manner the individual consumption of those articles of diet which might be considered to be important from the standpoint of sources of complete proteins, the extrinsic factor, vitamins and mineral elements, including iron. Thus, the data do not represent the chief sources of energy of the Puerto Rican diet but merely indicate those foodstuffs considered to be of special nutritional significance. The figures represent as nearly as could be determined the average number of times, without reference to quantity consumed, that the particular type of food mentioned was eaten during a period of one month. It is to be clearly understood that the figures are estimates and are necessarily of only approximate accuracy. From an inspection of the data, however, it is at once apparent that the consumption of meat, milk, eggs, whole grain cereals and butter was extremely low in many of these cases. Thus, meat, excluding chicken, was never eaten by 14 and was eaten only once a week or less frequently by 30 of the 63 patients. Eleven patients ate no eggs, and 18 consumed one egg or less a week. Thirty-five patients used no whole grain cereals, and 43 indulged in this type of food once a week or less frequently. Nineteen patients ate no butter. Milk was utilized mainly in small amounts in coffee unless indicated in the table by an asterisk. Fresh fish was rarely used, and the values in table 7 refer almost entirely to salt codfish. Green vegetables, such as lettuce, chard, string beans, chayote, okra and other Puerto Rican products, were largely employed in garnishing the main staples, rice and beans. Twenty patients were able to state the average daily cost of their food. The most expensive diet cost $1; the least expensive, 10 cents. The average daily expenditure for food was 33 cents, which

TABLE 7.—*Number of Times per Month, Without Reference to Quantity, That the Foods Listed Were Consumed by Patients with Sprue*

Case	Meat	Milk	Eggs	Fish	Whole Cereals	Green Vegetables	Fruit	Butter
1	12	0	0	0	0	30	30	4
2	1	8	8	20	0	4	6	0
3	30	30*	0	6	6	30	30	30
4	4	90*	30	1	1	4	30	4
5	0	60	12	1	0	12	30	0
6	4	90*	60	6	0	30	60	0
7	30	30	30	12	4	60	60	30
9	30	30	30	16	12	16	8	30
10	3	30	30	4	30	8	30	20
11	4	30	1	4	0	0	30	0
12	4	30	8	8	30	4	20	8
16	30	30	30	12	0	0	30	4
17	0	30	30	0	8	0	20	0
18	0	30	30	6	6	6	8	30
19	6	30	8	6	4	8	20	0
21	12	90	60	8	30	10	30	30
22	0	0	0	8	0	6	2	20
23	16	30	20	8	4	8	30	30
26	8	30	30	4	15	20	30	0
27	30	30	30	12	0	12	20	30
28	4	30	30	30	0	0	30	0
29	6	30	30	20	0	6	15	0
30	3	6	6	6	12	15	30	0
31	2	30	0	2	0	4	15	0
32	10	30	6	6	30	8	10	20
34	0	30	30	2	0	16	4	4
35	4	20	10	10	0	0	30	0
36	0	90*	30	0	0	0	20	0
37	4	30	90	0	20	0	30	..
39	4	10	3	30	8	30	30	0
42	8	8	12	8	0	0	30	12
44	30	30	30	0	0	8	45	0
48	4	30	30	0	0	0	30	30
49	20	30	30	30	30	30	45	30
50	20	30	60	0	30	30	30	12
51	40	30	30	4	2	30	60	12
52	25	30	16	0	0	40	40	..
53	6	60	12	8	30	30	2	30
54	5	60	0	1	0	2	60	30
55	0	20	0	0	0	0	10	..
57	0	30	30	0	0	30	60	30
59	8	30	30	6	0	10	15	..
61	6	30	1	0	0	8	40	0
62	16	40	60	0	0	12	30	8
63	4	0	0	30	0	15	10	..
64	0	60*	0	0	0	0	30	..
65	0	30	4	0	0	24	20	..
66	2	30*	30	0	3	10	30	..
67	30	60*	60	0	0	3	40	..
68	30	60*	15	4	30	20	40	0
69	2	60*	30	0	0	30	30	0
70	12	60	30	30	30	60	6	30
73	30	90*	240	4	4	10	15	..
74	20	0	30	4	12	12	40	..
75	0	30	0	0	0	30	30	8
77	0	90*	4	4	0	6	30	0
79	8	30	12	8	0	12	40	30
80	12	3	1	2	0	4	15	4
82	12	90*	10	12	0	0	10	8
84	16	30	0	12	12	4	60	30
85	12	30	16	6	30	12	16	2
86	0	30	4	4	4	0	16	..
89	0	90*	0	2	0	2	30	6

* This includes milk other than that used in coffee.

must have greatly exceeded the abilities of several patients whose daily bread was largely the offering of charitable neighbors.

Ashford,[81] whose long residence in Puerto Rico and painstaking study has given him an intimate knowledge of the dietary habits of the sufferer from sprue, has vividly described the situation. He has said in part:

> The Northern visitor to endemic centers in the tropics will usually find that, much against his will, he must consume an abnormally large quantity of greasy food. . . . He finds the native vegetables uncultivated, fibrous, and mawkish to his palate, and he seeks his calories, not in the tough, freshly-killed local beef, but in starches and sugars, the only familiar articles of diet at hand. We should here note the very well-known lack of nutritious fresh foods in certain tropical countries which, like Porto Rico, have to subsist on gold crops such as tobacco, coffee and sugar in order to support their enormous native populations. . . . Such peoples live chiefly on grain foods imported from the North; the laborer on highly polished rice, beans, and codfish, with a few rough tubers; the upper stratum on canned foods and a large variety of carbohydrates, pieced out with an inferior quality of milk and such vegetables as they can get from the meager local markets.

It is thus probable that the usual type of diet is such as to favor a diminished consumption of some of the known sources of the extrinsic factor, such as meat, eggs and whole grain cereals. Our recent parallel study [29] of the dietary histories of a group of patients with hookworm infection and anemia in Puerto Rico further attests the prevalence of defective nutrition in persons with anemia.

In this connection, it is interesting that in certain extreme instances of the general malnutrition of a group or community diarrheal conditions resembling sprue have been observed to become epidemic. In 1877 an epidemic of this type appeared during a famine in India. The postmortem appearance of the victims was carefully studied by Cunningham,[82] who reported atrophic changes in the mucosa of the small intestine and less marked alterations in the colon which are certainly suggestive of sprue. McCarrison [19] presented evidence of the importance of malnutrition in the etiology of "famine" and "jail" dysentery. Guarini [83] has reported 40 cases of gastro-enteritis followed by chronic enlargement of the abdomen among prisoners in the World War who were badly fed. Ashford [84] noted the appearance of sprue, pellagra and beriberi in association with deficient diet in Puerto Rico.

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81. Ashford, B. K.: Sprue, Ann. Clin. Med. **4**:13 (July) 1925.

82. Cunningham, D. D.: Fourteenth Annual Report of the Sanitary Commissioners with the Government of India, Calcutta, 1877.

83. Guarini, Carlo: Ricerche radiologiche sul cosi detto "grosso ventre di guerra" nei soldati reduci dalla prigionia, Riforma med. **36**:30 (Jan. 10) 1920.

84. Ashford, B. K.: Dietetic Deficiencies Predisposing to Sprue, Pellagra and Beri Beri in Porto Rico, Bull. Porto Rico M. A. **15**:249, 1921.

(*b*) Etiologic Significance of Defect of the Gastric (Intrinsic) Factor: On the other hand, a direct dietary defect of the extrinsic factor cannot be the entire cause of the condition of all patients with sprue because not all patients are improved by the addition of the extrinsic factor alone. The problem in this respect resembles that in addisonian pernicious anemia, in which the extrinsic factor in the usual amounts is rarely hematopoietically effective without the addition of the intrinsic factor. The observations on the tongues of patients with sprue in the early stages demonstrated that in certain instances the extrinsic factor was not effective until the intrinsic factor was added. In the advanced stage hematopoietic responses have demonstrated the same fact. It has been inferred from this that in certain patients with sprue a defect of the intrinsic factor exists, as in patients with pernicious anemia. In order to establish this point fully the content of intrinsic factor of the gastric juice of 3 patients with sprue was determined by observations of its hematopoietic effect, after contact with the extrinsic factor, on patients with addisonian pernicious anemia. These observations were carried out on patients at the Thorndike Memorial Laboratory of the Boston City Hospital with the collaboration of Dr. Maurice B. Strauss.

Patient 90 was an American planter from Puerto Rico with sprue of ten years' standing. Patient 91 was an American physician who had paid a yearly visit to Puerto Rico for many years but had had sprue for only a year. Patient 92 was an American minister from China who had suffered from sprue for seven years. In all 3 cases the use of diets for sprue containing beef muscle had been unsuccessful in controlling symptoms. The anemia in cases 90 and 92 was definitely macrocytic. In case 91 there was little anemia but severe diarrhea. The gastric contents of each of the patients contained free hydrochloric acid, and a test for pepsin made in cases 91 and 92 was positive (table 9). Assays for the intrinsic factor were made by methods already described,[62b] involving the daily administration of from 50 to 75 cc. of gastric contents from each patient with sprue, together with 200 Gm. of beef muscle, to suitable patients with pernicious anemia for a period of ten days. During subsequent periods of ten days normal human gastric juice in equal amounts was substituted for the gastric juice of the patients with sprue without other change in the conduct of the observation.

In table 8 are shown the detailed results of these observations. A reticulocyte response occurred in a suitable patient with pernicious anemia (test case C) as a result of the daily administration of 50 cc. of the gastric contents of patient 91 together with 200 Gm. of beef muscle. The subsequent administration of an equal quantity of normal human gastric juice under identical conditions did not produce

TABLE 8.—*Results of Tests on Patients with Pernicious Anemia of the Hematopoietic Effect of an Extract of the Liver of a Patient with a Fatal Case of Sprue, and of the Gastric Juice in Cases 90, 91 and 92 Administered with Beef Muscle*

Days	Test Case A: Extract △ 25 i. m., Liver of Case 81			Test Case B: Gastric Juice (Case 90) 75 Cc.; Beef Muscle, 200 Gm.			Test Case C: Gastric Juice (Case 91) 50 Cc.; Beef Muscle, 200 Gm.			Case 92: Beef Muscle, 200 Gm.			Test Case D: Gastric Juice (Case 92) 75 Cc.; Beef Muscle, 200 Gm.			Test Case E: Gastric Juice (Case 92) 50 Cc.; Beef Muscle, 200 Gm.		
	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent
First Period: Daily Administration of Various Substances as Indicated																		
0.....	1.28	32	0.1	1.46	29	**0.4**	0.98	27	1.0	1.65	**49**	0.8	1.05	28	0.6	1.12	25	**0.2**
2.....	1.26	32	0.2	1.24	30	**0.8**	0.81	23	1.0	1.32	37	0.2	1.07	24	0.8	1.10	25	0.4
4.....	1.01	30	0.2	1.04	30	2.0	1.01	24	2.0	1.68	37	1.4	0.87	23	0.6	1.11	25	1.4
6.....	1.00	30	0.1	1.09	30	1.0	0.83	30	7.6	1.52	39	**0.6**	0.91	25	**2.1**	1.06	25	2.8
8.....	0.88	27	0.6	1.18	28	0.6	1.18	33	**13.0**	1.45	37	1.2	0.97	31	1.5	1.10	25	**3.9**
10.....	....	..	...	1.12	30	2.2	1.25	35	10.8	1.28	35	**0.2**	....	..	...	0.92	25	2.4
Second Period: Daily Administration of Various Substances as Indicated																		
	Extract △ 25 i. m., Normal Liver			Normal Gastric Juice, 75 Cc.; Beef Muscle, 200 Gm.			Normal Gastric Juice 50 Cc.; Beef Muscle, 200 Gm.			Liver, 150 Gm.			Normal Gastric Juice, 75 Cc.; Beef Muscle, 200 Gm.			L. E. △ 200 p. o.		
0.....	0.88	27	0.6	1.12	30	2.2	1.25	35	10.8	1.28	35	0.2	0.97	31	1.5	0.92	25	**2.4**
2.....	1.28	36	2.0	1.36	30	1.6	**1.47**	37	3.4	1.04	35	1.0	0.79	32	2.8	1.19	**20**	0.2
4.....	1.21	34	1.2	1.22	28	2.8	1.55	40	1.6	1.19	32	5.0	1.22	28	5.8	1.45	**24**	**0.4**
6.....	1.33	34	3.4	1.26	30	6.8	1.79	50	2.2	1.34	36	**7.8**	0.92	30	14.0	1.14	27	6.8
8.....	1.47	35	**9.4**	1.45	36	12.4	1.81	50	2.8	**1.40**	35	2.4	1.39	40	**14.4**	1.17	27	**13.0**
10.....	1.52	39	9.0	1.67	43	**15.0**	2.40	59	0.6	1.40	32	3.4	1.82	45	10.2	1.37	28	7.0
12.....	1.57	42	5.6	2.09	47	7.0	2.18	58	1.4	....	..	...	1.65	52	6.2	....	..	...

a second rise of the reticulocyte count. On the contrary, no reticulocyte response was produced by the daily administration of 75 cc. of the gastric juice of patients 90 and 92, respectively, with 200 Gm. of beef muscle to each of 2 patients with pernicious anemia (test cases B and D). A reticulocyte response, however, promptly appeared in each patient with pernicious anemia (cases B and D) when equal quantities of normal human gastric juice were administered with beef muscle in immediately subsequent periods. A month after the first assay of the gastric juice of patient 92 for the intrinsic factor the test was repeated with 50 cc. of gastric contents and 200 Gm. of beef muscle daily, again with negative results.

From these direct observations on the effect of the gastric juice of patients with sprue on patients with pernicious anemia it is clear that the intrinsic factor was present in the gastric juice of patient 91 but not in that of patients 90 and 92, at least not in detectable amounts. As a control on the method of testing for the intrinsic factor, utilized in other patients with sprue in Puerto Rico, patient 92 was given 200 Gm. of beef muscle daily for a period of ten days, without producing a rise in the number of reticulocytes. The hematopoietic effect in pernicious anemia of the administration of 200 Gm. of beef muscle and 150 cc. of normal human gastric juice is about equal to that of 150 Gm. of prepared liver.[62b] Since the patient immediately thereafter responded to the daily administration of 150 Gm. of prepared liver with a rise in the reticulocyte count, it is clear that sufficient intrinsic factor was not present to produce a hematopoietic effect with the beef muscle. This result, then, agrees entirely with the negative result of the test involving a patient with pernicious anemia. These observations, taken with those made in Puerto Rico, are considered to constitute highly suggestive evidence that patients with sprue in both the early and the late stages may lack detectable amounts of the intrinsic factor usually absent in patients with addisonian pernicious anemia in relapse.

Thus, in sprue, as has been pointed out before for pernicious anemia,[62b] the chemical analysis of the gastric contents is found to be an inadequate index of the presence of the intrinsic factor. The presence of hydrochloric acid in the gastric contents in cases of sprue may be associated either with the presence (case 91) or with the absence (cases 90 and 92) of the intrinsic factor. With these reservations the results of chemical analysis of the gastric contents of 65 of our patients with sprue are shown in table 9. The results are also indicated for those patients in whom assays of the presence or absence of detectable amounts of the intrinsic factor were made by one of the methods

TABLE 9.—*Results of Analysis of Gastric Contents for Free Hydrochloric Acid, Pepsin and Intrinsic Factor*

Case	Titration of Free Hydrochloric Acid in Cc. N/10 Sodium Hydroxide			Peptic Activity after Egg White, Mm. per 24 Hr.	Intrinsic Factor
	After 7% Alcohol		After Histamine, 20 Min.		
	20 Min.	40 Min.			
1	0	0	0	0	..
2	0	0	38	8	+
3	66	70	84	5	..
4	90	96	97	16	..
5	45	49	67	14	+
9	0	0	18	8	+
10	43	30	48	6	..
12	0	0	8	8	..
15	83	78	93	9	0
16	0	0	33	9	..
17	5	8	54	11	+
19	0	0	0	..	+
21	0	0	3	8	..
22	0	0	0	0	±
23	40	13	83	7	..
26	8	0	38	8	..
28	38	50	70	10	..
29	0	0	13	19	..
30	0	0	0	0	..
31	0	0	0	9	+
32	5	11	0	9	0
34	25	45	62	11	..
35	0	0	0	6	±
36	0	9	0	5	..
37	0	0	0	4	±
38	13	31	63	7	..
39	0	0	0	2	..
40	0	0	80	10	..
42	41	20	78	10	+
44	0	0	0	0	..
45	0	0	0	5	..
47	10	18	53	0	..
49	0	0	0	0	+
50	15	0	43	8	..
51	0	0	0	0	..
52	14	5	15	12	..
53	0	0	0	0	..
54	0	0	0	0	..
55	0	0	3	7	..
56	20	55	83	6	..
57	0	0	0	2	..
59	0	0	23	6	..
60	0	0	0	6	..
61	30	25	60	8	..
64	8	29	35	10	..
65	0	0	4	8	..
68	28	25	39	6	+
70	4	0	10	9	..
72	0	0	0	5	..
74	25	15	24	6	..
75	0	0	0	6	..
76	0	0	32	10	..
79	5	40	72	9	+
80	15	1	23	7	..
81	0	0	0	4	..
82	24	45	78	15	..
83	17	35	71	..	..
84	0	0	30	8	..
85	33	24	0	8	..
86	5	5	40	13	±
87	0	0	0	..	..
88	50	0	57	24	..
90	32	37	40	..	0
91	7	12	17	11	+
92	27	53	70	10	0

described earlier. It is believed, however, on the basis of the work of Mettier and Minot,[85] that gastric anacidity may have a bearing on the absorption of iron from the upper intestinal tract and so may be of importance in predisposing the patient with sprue to the development of hypochromic anemia in certain instances.

Ashford [28] found achlorhydria in 39 per cent of 41 patients with sprue; Baumgartner and Smith,[37b] in one third of 15 patients, and Fairley and his associates,[86] in about 27 per cent of 26 patients. These values, obtained with broth or with Ewald test meals, correspond fairly well with our findings in 65 patients with sprue who were examined once, usually soon after coming under observation. In 33 (51 per cent) of our patients free hydrochloric acid was secreted in response to the ingestion of 50 cc. of 7 per cent alcohol; in 12 (18 per cent) acid was secreted only after the subcutaneous injection of 0.5 mg. of histamine phosphate, and in 20 (31 per cent) there was no secretion of hydrochloric acid. Estimations of pepsin were made by the use of Mett's tubes in the most acid sample of the gastric contents, which was, if necessary, brought to p_H 1.8 with hydrochloric acid. The egg albumin of the Mett tubes was coagulated at 85 C. In 7 of 18 patients in whom there was no secretion of free hydrochloric acid no pepsin was secreted. In only 1 of 8 patients in whom there was no secretion of pepsin was hydrochloric acid secreted. With 1 exception in all patients in whom there was secretion of free hydrochloric acid pepsin was also secreted.

(*c*) Etiologic Significance of Defects of Absorption: The variations in the responses of patients with pernicious anemia to orally administered liver extract are seemingly greater than those to parenterally administered material. Since in our experience the active principle of liver extract is not appreciably affected by autoclaving or by digestion with pepsin and hydrochloric acid or, according to Reimann, Sinek and Fritsch,[87] by digestion with trypsin or erepsin, it is probably not destroyed in the intestinal tract. On the other hand, the intrinsic factor especially might well be more susceptible to destruction [62b] by enzymes. The influence of difficulty in the absorption of hematopoietic substances

85. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, Am. J. M. Sc. **181**:25 (Jan.) 1931.

86. Fairley, N. H.; Mackie, F. P.; Chitre, G. D.; Gokhale, S. K.; Gore, S. N.; Malandkar, M. A., and Sacasa, F. J.: A Progress Report on Researches in Sprue (1924-1925), Indian J. M. Research **14**:105 (July) 1926.

87. Reimann, F.; Sinek, F., and Fritsch, F.: Untersuchungen zur Leberwirkung bei der Anaemia perniciosa, Ztschr. f. klin. Med. **41**:126, 1933.

in pernicious anemia has already been suggested.[88] It is, however, impossible to assert this as a proved fact because it is not known what are exactly comparable doses of liver extract both on oral and on parenteral administration. Even with parenterally administered liver extract the variation in response, due possibly to differences in its internal utilization in certain patients, may be as great as evidently exists with orally administered material. In this communication the effectiveness of the daily oral administration of liver extract derived from 300 Gm. of liver has usually been compared with the daily parenteral administration of an aqueous solution of this material derived from 10 Gm. of liver. From the observations of Minot and his associates [33a, b] it is clear that maximal reticulocyte responses are not usually obtained with this dosage of liver extract administered orally. On the other hand, prior to these observations on sprue it was discovered by Strauss, Taylor and Castle [89] that the daily parenteral administration of this material derived from 10 Gm. of liver will usually produce a reticulocyte response comparable to those obtained from the daily oral administration of liver extract derived from 600 Gm. of liver. Therefore, in these observations on sprue a trifling reticulocyte response to the daily oral administration of material derived from 300 Gm. of liver, even when followed by a large response to the daily parenteral administration of the same product derived from 10 Gm. of liver in a subsequent period, is not necessarily evidence of intestinal impermeability. Moreover, experience with pernicious anemia has shown that a certain proportion of the patients who are resistant to oral therapy are also resistant to a certain extent to parenteral therapy. At present, therefore, the existence of intestinal impermeability must remain only a logical possibility.

Observations on various types of anemia, however, favor such a supposition. Keefer and his associates [90] have shown that among patients with intestinal tuberculosis the degree of hypochromic anemia is greater in those who have diarrhea. The development of pernicious

88. (*a*) Schilling, V.: Gänsslens injizierbares Leberextrakt, Klin. Wchnschr. **10**:301 (Feb. 14) 1931. (*b*) Isaacs, Raphael; Sturgis, C. C.; Goldhamer, S. M., and Bethell, F. H.: The Use of Liver Extract Intravenously in the Treatment of Pernicious Anemia, J. A. M. A. **100**:629 (March 4) 1933. (*c*) Castle, Heath and Strauss.[62b]

89. Strauss, M. B.; Taylor, F. H. L., and Castle, W. B.: Intramuscular Use of Liver Extract: Maximal Responses of Reticulocytes from Daily Intramuscular Injection of Extract Derived from Ten Grams of Liver: Preliminary Communication, J. A. M. A. **97**:313 (Aug. 1) 1931.

90. Keefer, C. S.; Huang, K. K., and Yang, C. S.: The Importance of Undernutrition in the Production of Anemia Associated with Chronic Dysentery and Tuberculosis of the Intestine, Nat. M. J. China **15**:743, 1929.

anemia in patients with intestinal obstruction [91] or anastomosis of the small intestine [92] has been reported. In sprue the changes in the microscopic appearance of the intestinal wall are suggestive of dysfunction, and in this condition as well as in celiac disease [93] and chronic diarrhea of various types [94] there is evidence of a disturbance of the absorption of fat and of inorganic elements. Thus, the fatty stools and occasional tetany of sprue are not based on any definite evidence of parathyroid or pancreatic deficiency [95] but correspond to the findings in diarrheal conditions, such as celiac disease, in which split fats and calcium are not well absorbed or are lost in the stools in excessive amounts.[93] In a disease in which diarrhea and evidence of gastro-intestinal disturbance exist to the extent encountered in sprue and in which fats and calcium are clearly not always well absorbed, it is not unnatural to believe that difficulty in the absorption of hematopoietic substances may occur. If not due to changes in the intestinal wall this effect could result from the diarrhea.

A common history in our patients was that formerly a diet for the treatment of sprue had relieved the symptoms or improvement had taken place and had been maintained with a given amount of liver extract orally administered. By the time they were observed by us, diets for sprue and oral therapy with liver extract were no longer as effective as they had been. The statements of some of these patients were confirmed by observations under controlled conditions. In no instance, however, was relief not forthcoming with sufficient amounts of parenterally administered liver extract. Although it is impossible to state whether an original dosage of parenterally administered material would not have become proportionately inadequate, this fact is suggestive of

91. Faber, Knud: Perniciöse Anämie bei Dünndarmstricturen, Berl. klin. Wchnschr. **34**:643 (July 26) 1897. Meulengracht, E.: Pernicious Anemia in Intestinal Stricture, with Report of One Liver-Treated Case, Acta med. Scandinav. **72**:231, 1929.

92. Little, W. D.; Zerfas, L. G., and Trusler, H. M.: Chronic Obstruction of the Small Bowel: Result of Two Entero-Enterostomies and Apparently the Cause of Pernicious Anemia, J. A. M. A. **93**:1290 (Oct. 26) 1929. Castle, Heath and Strauss.[62b]

93. Bennett, T. I.; Hunter, Donald, and Vaughan, J. M.: Idiopathic Steatorrhoea (Gee's Disease): A Nutritional Disturbance Associated with Tetany, Osteomalacia and Anaemia, Quart. J. Med. **1**:603, 1932.

94. Linder, G. C., and Harris, C. F.: Calcium and Phosphorus Metabolism in Chronic Diarrhoea with Tetany, Quart. J. Med. **23**:195 (Jan.) 1930.

95. Ashford, B. K., and Hernández, L. G.: Blood-Serum Calcium in Sprue and Other Pathologic States in the Tropics, Am. J. M. Sc. **171**:575 (April) 1926. Sokhey, S. S., and Malandkar, M. A.: Pancreatic Function in Sprue, Indian J. M. Research **15**:921 (April) 1928.

a progressive difficulty with the absorption of hematopoietic substances. The following history is illustrative:

When first under observation patient 92 responded to the daily oral administration of 150 Gm. of liver. Subsequently the blood values approached normal as a result of the daily ingestion of liver extract derived from 300 Gm. of liver. A year later, however, the patient reentered the hospital because despite the daily ingestion of liver extract derived from 600 Gm. of liver the red blood cells had declined to a level of about 1,000,000 per cubic millimeter. Under observation in the hospital the daily oral administration for ten days of the same amount of liver extract produced a very slight reticulocyte response (table 4). A single intravenous injection of liver extract derived from 100 Gm. of liver, however, at once produced a large

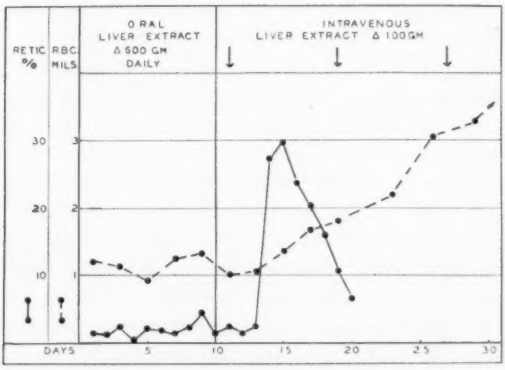

Chart 2.—A comparison of the hematopoietic effects of liver extract administered orally and then parenterally in case 92. The large daily oral dose of liver extract derived from 600 Gm. of liver was without significant hematopoietic effect, in contrast to the striking effect of a single intravenous injection of the same extract derived from 100 Gm. of liver. This probably indicates an abnormal degree of intestinal impermeability to hematopoietic substances.

reticulocyte response, and the blood values rose rapidly. These results are graphically portrayed in chart 2. Since that time, for three years, this patient has remained in excellent health with regular intramuscular injections of liver extract.

It would simplify our concept of the mechanism of the disease if the progressive changes in the effectiveness of oral therapy could be attributed with certainty to an increase in intestinal impermeability. For the reasons stated earlier, this cannot be done. Nevertheless, an arbitrary standard has been applied to the observations on these patients in an attempt to indicate in which cases, in our opinion, the suspi-

cion of intestinal impermeability was most justified. If the reticulocyte response to the daily oral administration of liver extract derived from 300 Gm. of liver or more was less than one third of that expected in similar patients with pernicious anemia,[33a, b] and if the reticulocyte response to the subsequent daily parenteral injection of the same liver extract derived from 10 Gm. of liver was greater than two thirds of this expected value, the patient was considered arbitrarily to have some degree of intestinal impermeability. On the basis of these standards, patients 40, 44, 54, 86 and 92 are considered to fulfil the requirements. This conclusion should, however, be accepted with all the reservations set forth in the foregoing discussion of the difficulties of the problem.

(*d*) Deficiency of Hematopoietic Substance in the Liver in a Fatal Case of Sprue with Severe Macrocytic Anemia: Richter, Ivy and Kim[96] have found that extracts of the livers of patients who die of pernicious anemia in relapse do not contain hematopoietic substances, at least in the amounts present in the livers of normal persons. If the mechanisms of deficiency in sprue outlined previously resemble those in addisonian pernicious anemia, the livers of patients with sprue and severe macrocytic anemia should be similarly deficient.

A test of this fact was made on the occasion of the death of a patient with sprue and severe anemia (case 81). The patient's condition was so grave on admission to the hospital that he died twenty-four hours later despite an injection of liver extract derived from 100 Gm. of liver and a transfusion of 300 cc. of blood. At autopsy the observations were typical of uncomplicated sprue.

An extract of the patient's liver suitable for parenteral injection was therefore made. Seven hundred and sixty grams of liver pulp was placed in 2,500 cc. of cold water and vigorously stirred for half an hour. Concentrated hydrochloric acid was added to bring the mixture to p_H 5. It was then boiled for five minutes and placed in the icebox for twelve hours. The original 2,000 cc. of filtrate and the second filtrate derived from a resuspension of the residue in 2,000 cc. of water at p_H 5 were combined and evaporated to dryness at 60 C. The precipitate was taken up in 1,000 cc. of 70 per cent alcohol, a small undissolved residue being washed again with 200 cc. of 70 per cent alcohol. The 1,200 cc. of combined filtrates was evaporated to 320 cc. at 60 C. To this filtrate was added sufficient absolute alcohol to reach a concentration of 95 per cent by volume. Six hundred cubic centimeters of ether was then added, and sedimentation was allowed to take place in the icebox. The precipitate was later dried at 60 C. and was found to amount to 28.21 Gm. of a whitish-yellow powder. The liver of a

96. Richter, O.; Ivy, A. C., and Kim, M. S.: Action of Human "Pernicious Anemia Liver Extract," Proc. Soc. Exper. Biol. & Med. **29**:1093 (June) 1932.

patient without anemia who died of acute cardiac dilatation was identically treated with the same original amount of liver pulp and reagents.

The extracts made of the livers of patient 81 and of the control patient were dissolved in water, neutralized and sterilized by Berkefeld filtration. The volume of each solution was such that 20 cc. of each contained the material derived from 100 Gm. of liver pulp. Into a suitable patient with pernicious anemia (test case *A*) was injected daily for eight days 5 cc. of the extract, which was the amount derived from 25 Gm. of the liver of patient 81. No significant reticulocyte response occurred (table 8). During an immediately subsequent period of twelve days 5 cc. of the extract derived from 25 Gm. of the liver of the control patient was injected daily. This produced a peak of the reticulocyte count on the eighth day of 9.4 per cent. In a subsequent period of ten days (not shown in table 8) the amount of liver extract derived from 25 Gm. of animal liver was injected daily, without a further reticulocyte response. Thus, the liver of the patient who died of sprue and severe macrocytic anemia did not contain detectable amounts of hematopoietic substance, in contrast to the liver of the control subject without anemia. This result further substantiates the evidence for a resemblance between the fundamental deficiency in sprue with macrocytic anemia and that in addisonian pernicious anemia.

(*e*) Etiologic Significance of Accessory Deficiency of Iron to the Anemia: From the observations of several workers [97] it is evident that the anemia of sprue may be either macrocytic or hypochromic. The resemblance of the macrocytic type of anemia of sprue to the blood picture of pernicious anemia has been pointed out by others [98] and confirmed by the present observations. Even in pernicious anemia, however, the blood picture is not so constant as was commonly supposed. Now that the diagnosis and the physiologic responses of pernicious anemia can be studied by means of liver extract it is clear that classic uniformity of the blood picture is not always present. Indeed, the anemia typical of the syndrome described by Thomas Addison merges by a series of rarer intermediate forms with that of idiopathic hypochromic anemia with gastric anacidity.[99] It is known that pernicious anemia in responding to liver extracts may assume the characteristics of hypochromic anemia

97. Ashford.[28] Fairley, Mackie and Billimoria.[42] Baumgartner.[43]

98. Baumgartner and Smith.[37b] Reed and Wyckoff.[38] Musser.[40] Fairley, Mackie and Billimoria.[42]

99. (*a*) Wilkinson, J. F., and Brockbank, William: The Importance of Familial Achlorhydria in the Aetiology of Pernicious Anaemia, Quart. J. Med. **24**:219 (Jan.) 1931. (*b*) Heath, C. W.: The Interrelation of Pernicious Anemia and Idiopathic Hypochromic Anemia: The Study of a Family in Which Both Conditions Occurred Singly and Combined, Am. J. M. Sc. **185**:365 (March) 1933. Faber and Gram.[53]

and require iron therapy for complete remission.[100] Heath[99b] has recently studied the members of a family in which appeared types of anemia initially resembling pernicious anemia or hypochromic anemia, respectively. He was able to convert one type into the other by the appropriate use of either liver extract or iron over considerable periods of time. The physiologic concept here encounters no such difficulties as are imposed by the limitations of a rigid nosologic classification. It merely supposes that by a suitable proportion of deficiency of "liver extract," of "iron," and possibly of other substances the morphology of anemias ranging from macrocytic through normocytic to microcytic and hypochromic may be produced. Its supporters can demonstrate that the physiologic response of these differing types of anemia are dependent on the differing nature of the deficiency involved.[101]

The findings in the blood of 40 patients with pernicious anemia mostly in the first relapse have been contrasted with those for the 92 patients with sprue in table 2. Probably owing to the selection for macrocytic anemia exercised in choosing the patients with sprue, only 6 patients had a color index of less than unity, and of those only 2 had a mean corpuscular volume of less than the normal for the method. Otherwise, as mentioned previously, the blood picture of the patients with sprue was typical of pernicious anemia. The obviously defective diets of many of these patients with sprue resembled somewhat those of a parallel series of patients with hookworm disease and hypochromic anemia studied in Puerto Rico.[29] The 54 patients with hypochromic anemia showed an incidence of gastric anacidity (24 per cent) only slightly less than that observed in the 65 patients with sprue (31 per cent). Of 47 patients with hookworm disease who were adequately studied, 8 gave a history or showed evidence of lingual changes and 24 had had moderately severe diarrhea. Thus, the distinction between sprue with hypochromic anemia and hookworm disease with lingual and intestinal symptoms was necessarily arbitrary in some instances. In the same community hypochromic anemia without hookworm infection, which responded readily to therapy with iron, was common. In patients with addisonian pernicious anemia, whose diet is relatively good, perhaps the highest incidence of a uniformly macrocytic anemia is found. On the other hand, as the factor of dietary deficiency or of intestinal disturbance becomes more pronounced the possibility of a defect of iron metabolism becomes greater and the

100. Beebe, R. T., and Lewis, G. E.: The Maintenance Dose of Potent Material in Pernicious Anemia, Am. J. M. Sc. **181**:796 (June) 1931.

101. Watkins, C. H.: Classification of Idiopathic Secondary Anemia, Proc. Staff Meet., Mayo Clin. **4**:19, 1929. Davies, D. T.: Studies on Achlorhydria and Anaemia, Quart. J. Med. **24**:447 (July) 1931. Minot and Heath.[33d]

TABLE 10.—*Results of the Administration of Ferric Ammonium*

Days	Autolyzed Yeast, 60 Gm. Case 2				Autolyzed Yeast, 120 Gm. Case 9				Beef Muscle, 300 Gm.; Milk, 1,500 Cc. Case 17				Beef Muscle, 300 Gm.; Milk, 1,500 Cc. Case 19				L. E. △ 100 i.m. Every 10 Days Case 30			
	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent
First Period: Administration of Various Substances as Indicated																				
0	1.56	32	1.02	3.4	1.98	53	1.33	1.2	2.56	75	1.47	1.2	1.55	36	1.16	0.6	1.35	41	1.52	2.8
2	1.85	33	0.89	1.8	2.00	51	1.27	0.8	2.46	72	1.46	1.0	1.23	32	1.30	1.0	1.35	35	1.30	0.8
4	1.73	34	0.98	2.8	2.48	58	1.16	2.6	2.66	81	1.52	2.4	1.21	30	1.24	2.6	1.43	45	1.57	9.8
6	1.45	35	1.20	7.8	2.12	56	1.32	4.0	2.68	79	1.47	3.6	1.22	32	1.31	3.0	1.53	48	1.57	22.2
8	1.69	38	1.12	8.4	2.25	56	1.22	6.8	2.70	79	1.46	4.4	1.19	30	1.26	3.6	1.93	49	1.27	12.2
10	1.72	35	1.01	**12.8**	2.42	60	1.24	**8.2**	2.96	77	1.30	**4.6**	1.25	32	1.28	2.2	1.74	41	1.18	5.4
12	1.81	38	1.04	4.6	2.39	56	1.17	5.4	3.20	78	1.21	2.6	1.24	32	1.29	2.0	2.15	47	1.09	5.8
14	2.01	38	0.94	3.6	2.36	57	1.21	2.4	....	..	....	...	1.07	26	1.21	1.6	2.18	50	1.15	4.8
16	1.77	36	1.01	4.8	2.15	54	1.26	1.8	2.88	78	1.35	3.4	1.14	26	1.14	2.0	....	..	....	...
18	1.98	37	0.93	3.8	2.37	62	1.32	2.0	3.37	82	1.21	1.8	1.32	27	1.02	2.0	....	..	....	...
20	2.10	38	0.90	3.4	2.59	66	1.27	2.4	....	..	....	...	1.11	29	1.31	1.8	2.18	49	1.12	6.0
22	L. E. △ 300 p.o. Daily				2.71	74	1.37	1.8	2.81	73	1.30	1.0	1.14	25	1.10	1.6	....	..	....	...
24	2.19	39	0.89	4.6	2.51	67	1.33	3.0	2.88	73	1.27	2.0	L. E. △ 300 p.o. Daily				....	..	....	...
26	1.92	46	1.19	**5.4**	2.50	59	1.18	**1.2**	2.90	70	1.21	1.4	1.06	27	1.27	3.4	2.77	59	1.07	1.2
28	1.79	41	1.14	3.0	2.23	56	1.26	4.4	L. E. △ 300 p.o. Daily				1.01	26	1.29	4.2	....	..	....	...
30	2.49	40	0.80	3.6	L. E. △ 300 p.o. Daily				3.10	64	1.03	3.2	1.19	29	1.22	2.4	....	..	....	...
32	L. E. △ 10 i.m. Daily				1.98	54	1.36	1.8	3.20	65	1.02	1.0	1.28	26	1.02	1.6	2.81	56	1.00	1.2
Weeks													L. E. △ 10 i.m. Daily							
5	2.59	44	0.84	3.8	1.66	46	1.39	2.0	3.39	69	1.02	1.2	1.02	26	1.27	4.0	2.51	58	1.16	1.0
	L. E. △ 300 p.o. Daily				L. E. △ 10 i.m. Daily				L. E. △ 10 i.m. Daily											
6	2.51	37	0.73	2.4	1.67	48	1.44	1.4	3.46	62	0.90	2.0	1.08	25	1.16	**15.8**	3.42	57	0.83	1.0
7	2.94	40	0.68	...	2.38	53	1.11	2.0					1.50	26	0.87	4.8	3.39	60	0.89	0.8
					L. E. △ 50 i.m. Daily															
8	....	..	....	...	2.33	48	1.03	3.6	....	..	....	...	....	..	....	...	3.11	50	0.80	...
9	2.79	44	0.78	...					....	..	....	...	....	..	....	...				
Second Period: Administration of Ferric Ammonium Citrate as Indicated																				
	Ferric Ammonium Citrate, 6 Gm. Daily				L. E. △ 50 i.m. Daily Ferric Ammonium Citrate, 6 Gm. Daily				L. E. △ 10 i.m. Daily Ferric Ammonium Citrate, 6 Gm. Daily				Ferric Ammonium Citrate, 6 Gm. Daily				Ferric Ammonium Citrate, 6 Gm. Daily			
0	2.79	44	0.78	...	2.33	48	1.03	3.6	3.46	62	0.90	2.0	1.50	26	0.87	4.8	3.11	50	0.80	...
2	....	..	....	...	2.35	44	0.94	3.8	3.28	66	1.01	3.8	1.58	23	0.73	6.4	....	..	....	...
4	3.65	54	0.74	...	2.42	43	0.89	5.2	3.00	64	1.07	**5.6**	1.97	26	0.66	**10.4**	....	..	....	...
6	....	..	....	...	2.15	47	1.09	5.0	3.36	64	0.95	5.4	1.96	30	0.77	7.2	....	..	....	...
8	3.87	49	0.63	...	2.35	48	1.02	**7.6**	Ferric Ammonium				2.18	33	0.76	5.6	3.60	56	0.78	...
10	....	..	....	...	2.58	48	0.93	6.0	Citrate, 6 Gm. Daily				1.83	30	0.82	2.0	....	..	....	...
12	3.96	53	0.67	...	2.31	49	1.06	3.0	....	..	....	...	L. E. △ 50 i.m. Daily				....	..	....	...
14	....	..	....	...	....	..	....	...	4.90	79	0.81	3.0	2.06	39	0.95	1.0	....	..	....	...
Weeks																				
3	3.87	67	0.87	...	3.37	69	1.02	1.6	....	..	....	...	1.92	36	0.94	1.8	3.90	65	0.83	...
4	4.11	64	0.78	...	3.25	61	0.94	2.2	....	..	....	...	2.36	35	0.74	3.6	3.56	64	0.90	...
5	....	..	....	...	3.54	67	0.95	...	4.75	81	0.85	1.4	2.55	38	0.75	...	L. E. △ 300 p.o. Daily Ferric Ammonium Citrate, 6 Gm. Daily			
					L. E. △ 300 p.o. Daily Ferric Ammonium Citrate, 6 Gm. Daily															
6	....	..	....	...	....	..	....	...	....	..	....	...	....	..	....	...	4.32	67	0.79	1.6
7	4.40	68	0.77	1.0	3.17	70	1.10	...	....	..	....	...	....	..	....	...	4.08	66	0.81	0.8
8	....	..	....	...	....	..	....	...	....	..	....	...	....	..	....	...	4.09	64	0.78	...
9	4.53	75	0.83	0.6	3.52	71	1.01	...	....	..	....	...	....	..	....	...	3.74	64	0.86	...
10									....	..	....	...	....	..	....	...				

L. E. △ 10 i.m. Daily Case 34				L. E. △ 100 i.m. Once Case 43				L. E. △ 300 p.o. Daily Case 52				L. E. △ 300 p.o. Daily Case 61				L. E. △ 10 i.m. Daily Case 79			
Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent
First Period: Administration of Various Substances as Indicated																			
2.78	55	0.99	2.4	0.55	17	1.55	0.6	2.76	56	1.01	6.8	0.91	26	1.43	5.8	1.25	35	1.40	0.4
2.79	58	1.04	3.0	0.65	18	1.38	...	....	..	....	...	0.73	25	1.71	8.0	1.70	39	1.15	3.8
2.98	58	0.97	2.8	0.66	18	1.36	10.0	....	..	....	...	0.83	25	1.51	10.0	1.62	40	1.23	5.2
3.12	64	0.87	2.0	0.56	23	2.05	**17.0**	....	..	....	...	0.79	25	1.58	8.4	1.56	40	1.28	**9.2**
3.38	57	0.84	3.0	**0.80**	25	1.56	14.8	3.14	49	0.78	1.6	0.90	27	1.50	9.2	1.51	42	1.39	8.4
3.18	55	0.87	2.8	0.79	25	1.58	9.2	....	..	....	...	1.06	33	1.56	**15.0**	1.55	46	1.48	4.8
2.88	55	0.97	1.6	0.79	26	1.65	5.4	....	..	....	...	0.87	35	2.01	12.0	1.51	44	1.46	2.6
3.23	58	0.90	2.4	1.06	27	1.28	4.8	3.51	47	0.66	0.6	0.86	30	1.74	7.2	1.58	44	1.39	3.4
L. E. △ 50 i.m. Daily				0.72	26	1.81	9.0	....	..	....	...	L. E. △ 10 i.m. Daily				1.69	47	1.39	3.8
2.85	55	0.96	3.0	1.23	30	1.22	7.0	....	..	....	...	0.98	34	1.73	4.8	1.71	47	1.37	5.2
3.00	52	0.86	2.0	1.50	34	1.13	8.0	....	..	....	...	1.10	34	1.55	5.0	1.91	52	1.36	2.2
2.92	48	0.82	2.2	1.65	33	1.00	6.0	2.95	45	0.76	...	1.17	37	1.58	6.6	**2.14**	51	**1.19**	2.2
				1.45	35	1.21	6.6	....	..	....	...	1.15	39	1.70	**7.2**	1.97	49	**1.24**	3.0
....	..	....	...	1.65	35	1.06	3.8	....	..	....	...	1.26	39	1.55	3.8	1.89	51	1.35	3.4
....	..	....	...	1.71	35	1.02	4.6	3.65	48	0.65	0.4	....	..	....	...	2.31	56	1.21	2.4
....	..	....	...	2.13	34	0.80	2.0	....	..	....	...	1.57	42	1.34	3.0	2.23	55	1.23	2.0
....	..	....	...	2.60	39	0.75	2.6	....	..	....	...	....	..	....	...	2.36	60	1.27	2.4
....	..	....	...	2.24	37	0.83	2.0	3.20	47	0.73	0.2	2.25	45	1.00	...	2.45	57	1.16	5.4
				L. E. △ 300 p.o. Daily															
....	..	....	...	2.80	40	0.71	1.2	3.56	47	0.66	1.2	2.64	50	0.95	...	2.74	64	1.17	1.2
....	..	....	...	2.97	41	0.69	0.8	3.21	45	0.70	...	2.41	49	1.02	...	2.77	65	1.17	1.2
....	..	....	...	....	..	....	...	....	..	....	...	....	..	....	...	3.34	67	1.00	...
....	..	....	...	....	..	....	...	....	..	....	...	....	..	....	...	3.15	69	1.10	...

Second Period: Administration of Ferric Ammonium Citrate as Indicated

L. E. △ 50 i.m. Daily Ferric Ammonium Citrate, 6 Gm. Daily				Ferric Ammonium Citrate, 6 Gm. Daily				Ferric Ammonium Citrate, 6 Gm. Daily				Ferric Ammonium Citrate, 6 Gm. Daily				Ferric Ammonium Citrate, 6 Gm. Daily			
2.92	48	0.82	2.2	2.97	41	0.68	0.8	3.21	45	0.70	...	2.41	49	1.02	...	3.15	69	1.10	...
2.90	51	0.88	2.6	3.26	43	0.66	0.6	....	..	....	...	....	..	....	...	3.33	72	1.08	1.6
2.89	53	0.92	3.4	3.23	44	0.68	1.4	....	..	....	...	2.43	48	0.99	...	3.30	68	1.03	1.0
2.84	55	0.97	**6.8**	3.78	39	0.52	1.6	....	..	....	...	....	..	....	...	3.60	75	1.04	1.0
3.49	59	0.85	6.0	3.14	43	0.68	1.2	3.80	50	0.66	1.4	2.60	53	1.02	...	3.39	73	1.08	0.6
2.93	57	0.97	6.4	3.24	46	0.71	**5.8**	....	..	....	...	....	..	....	...	....	..	....	...
3.81	64	0.84	5.0	3.36	50	0.74	3.0	....	..	....	...	2.78	54	0.97	...	....	..	....	...
....	..	....	...	....	..	....	...	4.47	53	0.59	1.0	....	..	....	...	....	..	....	...
Ferric Ammonium Citrate, 6 Gm. Daily																			
4.09	71	0.89	1.4	....	..	....	...	4.40	56	0.64	...	2.70	50	0.93	...	4.01	76	0.95	...
4.41	71	0.80	0.6	....	..	....	...	....	..	....	...	2.99	52	0.87	...	....	..	....	...
												Add L. E. △ 20 i.m. Daily							
4.53	75	0.83	...	....	..	....	...	....	..	....	...	2.46	53	1.08	...	....	..	....	...
4.81	80	0.83	...	....	..	....	...	....	..	....	...	3.04	58	0.95	...	3.82	80	1.05	...
4.85	83	0.86	...	....	..	....	...	....	..	....	...	3.29	65	0.99	...				
				....	..	....	...	....	..	....	...	3.62	63	0.87	...	....	..	....	...
....	..	....	...	....	..	....	...	....	..	....	...	3.43	67	0.98	...	....	..	....	...
....	..	....	...	....	..	....	...	....	..	....	...	3.70	72	0.97	...	....	..	....	...

finding of hypochromic anemia becomes more common, as in pellagra,[92a] celiac disease,[93] chronic dysentery[90] or sprue.[28]

The frequent appearance of hypochromic anemia in sprue clearly suggests the possible influence of some degree of "iron" deficiency on the anemia in combination with the effects of the "liver extract" deficiency leading to lingual and gastro-intestinal symptoms and to macrocytic anemia. In a few patients with a low initial color index (cases 11, 28, 29, 41 and 87) the lingual and gastro-intestinal symptoms were promptly relieved by liver extract, but the blood values were not significantly improved until therapy with iron was begun. In many patients as the remission achieved by effective liver extract therapy progressed the color index and mean corpuscular volume diminished and in some instances became distinctly less than normal. In these patients

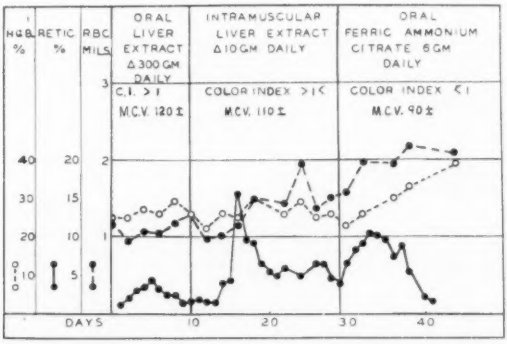

Chart 3.—A comparison of the hematopoietic effects of the daily oral administration in case 19 of liver extract derived from 300 Gm. of liver and the daily parenteral administration of the same liver extract derived from 10 Gm. of liver. The third reticulocyte response indicates the effect of ferric ammonium citrate given after the color index had become less than 1 and the mean corpuscular volume had decreased from about 120 to 90 cubic microns as a result of therapy with liver extract.

the upward progress of the blood values then became very slow despite liberal administration of liver extract. Thereupon the administration of iron salts with or without the continuation of liver extract therapy produced improvement in the blood values, occasionally associated with definite reticulocyte responses.

An illustration of the effectiveness of iron salts on 10 patients with sprue is presented in table 10. In cases 34 and 52 the color index at the beginning of the observation was close to unity, and intramuscular and oral liver extract therapy resulted only in a progressive fall of the color index at the expense of the hemoglobin, with little increase

in the number of red blood cells over periods of twenty-two days and seven weeks, respectively. The administration of 6 Gm. of ferric ammonium citrate daily then led to a definite increase in reticulocytes with a progressive increase in blood values in case 34. In case 52, as a result of iron therapy, the hemoglobin value, which had been stationary for six weeks, increased 8 per cent and the red blood cells increased over a million per cubic millimeter in fourteen days. Unfortunately, at this time the patient felt so much improved that she desisted from coming to the clinic. The other patients showed in varying degrees a progressive fall of the color index with effective liver extract therapy, a tendency of the red blood cell and hemoglobin values to become stationary and an acceleration of progress from the administration of iron. In cases 9, 17, 19 and 43 the effectiveness of the iron therapy was signalized by a definite increase in reticulocytes. The results of the observations in case 19 are graphically shown in chart 3. In case 79 the blood level was probably too high for a reticulocyte response to occur, although in this case, as in cases 2, 30 and 61, in which reticulocyte counts were not made, the augmentation of the red blood cell and hemoglobin values under therapy with iron is apparent. In numerous other instances, although less clearly demonstrable, it became apparent that the prolonged use of both liver extract and iron was necessary in order to restore the blood values to normal. The same therapeutic necessity has already been demonstrated to exist in certain cases of addisonian pernicious anemia [100] and in cases of pernicious anemia of pregnancy.[67] It is, moreover, possible that the deficiency of both liver extract and iron shown to exist in many of these patients was responsible for the fact that the hematopoietic responses of the patients to liver extract were usually not so marked as those of patients with addisonian pernicious anemia. This fact will be discussed under the treatment of the anemia.

The Experimental Production in Animals of Conditions Resembling Sprue by Means of Deficient Diets.—Although McCarrison [19] made no references to sprue as a result of his experiments on animals, the disturbances of the gastro-intestinal tract produced by him with defective diets in pigeons, guinea-pigs and, especially, monkeys suggested to Elders [18] analogies with the disturbances in patients with sprue and are even more interesting in retrospect. McCarrison summarized the symptoms in his animals as follows: "Distaste and loathing of the food, loss of appetite, depraved appetite, vomiting, diarrhea, dysentery, anemia, loss of weight, low body temperature, cardiovascular depression, asthenia, and loss of health of the skin." He made no mention of observations on the tongue but noted congestive, necrotic and inflammatory changes of the entire gastro-intestinal tract, inclusive of the

secretory elements in the mucosa. In 1917 Chittenden and Underhill [102] produced an acute syndrome in dogs which they suggested might be analogous to the condition in pellagra. Necrosis and gangrene of the tongue and buccal membranes together with bloody diarrhea occurred. The upper portion of the esophagus was affected, but aside from congestion a microscopic examination of the intestinal tract revealed relatively minor changes of an atrophic character. Peas and lean meat, included in the diet, delayed the onset of the symptoms, and subsequently Underhill and Mendel [103] discovered that the syndrome could be relieved by a number of substances containing carotene. No mention of the findings in the blood was made. Goldberger and his associates [104] produced a somewhat similar disease in dogs fed diets resembling those of human beings with pellagra. The clinical features of the disease were those of a short illness marked by stomatitis, salivation, diarrhea and, in some instances, dermatitis. Denton [105] has stated that the pathologic changes resemble closely those of human pellagra. He characterized the lesions as of a degenerative type affecting the superficial connective tissue of the mucous and dermal membranes, respectively. The mouth, including the tongue, and the pharynx, esophagus, intestine and skin of the scrotum were affected. Thus, experimental evidence is not wanting that a defective diet in animals may produce lingual and gastrointestinal symptoms of an acute type together with histologic changes which have been stated to resemble the lesions in pellagra. The manifestations of the disease produced in dogs by Goldberger and his associates could be prevented or cured by use of sources of the extrinsic factor (meat or yeast)[104b] or by liver extract.[106] It appears to us, however, that if the cutaneous lesions are excepted the resemblance of these conditions to pellagra is no greater than their resemblance to sprue.

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102. Chittenden, R. H., and Underhill, F. P.: The Production in Dogs of a Pathological Condition Which Closely Resembles Human Pellagra, Am. J. Physiol. **44**:13 (Aug.) 1917.

103. Underhill, F. P., and Mendel, L. B.: A Dietary Deficiency Canine Disease—Further Experiments on the Diseased Condition in Dogs Described as Pellagra-Like by Chittenden and Underhill and Possibly Related to So-Called Black Tongue, Am. J. Physiol. **83**:589 (Jan.) 1928.

104. (*a*) Goldberger, Joseph, and Wheeler, G. A.: Experimental Black Tongue of Dogs and Its Relation to Pellagra, Pub. Health Rep. **43**:172 (Jan. 27) 1928. (*b*) Goldberger, Joseph; Wheeler, G. A.; Lillie, R. D., and Rogers, L. M.: A Further Study of Experimental Blacktongue with Special Reference to the Blacktongue Preventive in Yeast, ibid. **43**:657 (March 23) 1928.

105. Denton, James: A Study of the Tissue Changes in Experimental Black Tongue of Dogs Compared with Similar Changes in Pellagra, Am. J. Path. **4**:341 (July) 1928.

106. Goldberger, Joseph, and Sebrell, W. H.: The Blacktongue Preventive Value of Minot's Liver Extract, Pub. Health Rep. **45**:3064 (Dec. 12) 1930.

In the experiments so far cited little if any attention was paid to possible changes of the blood. In 1932 Wills and Billimoria [107] reported the production in young monkeys of a macrocytic type of anemia with megaloblastic hypertrophy of the bone marrow apparently curable with marmite, a preparation of autolyzed yeast, or with liver extract. This anemia resembled the macrocytic anemia of pregnant women in India and was curable by the same therapeutic agents.[83] The diet of the monkeys was based on the usual diet of these patients. No mention of lingual symptoms was made; diarrhea occurred in one monkey. The suggestion afforded by the observations made in Puerto Rico caused Rhoads to become interested in the possible resemblances between black tongue in dogs and sprue. Rhoads and Miller [52b] placed dogs on diets resembling those used by Goldberger and his associates [104a] in the production of black tongue. After about six weeks changes in the mouth and tongue were observed. Atrophy of the lingual papillae of the anterior and lateral aspects of the tongue occurred. Subsequently irregular diarrhea, occasionally accompanied with the passage of blood, developed. Periods of semisolid voluminous yellow stools alternated with periods of normal stools. Marked loss of weight occurred, although the diet was taken fairly well except when stomatitis and salivation were severe. By means of short intervening periods of normal diet the fatal outcome was delayed. As time passed anemia developed, which was, in certain animals, macrocytic. The extent and degree of activity of the femoral bone marrow became markedly increased, and in certain animals the hyperplasia was predominantly megaloblastic. Gastric anacidity occurred as a terminal event in a few animals. Yeasts were cultivated from the stools of about 10 per cent of the affected animals. Thus, in many respects the clinical picture and findings in the blood and bone marrow were similar to those described as occurring in sprue.

The symptoms and the anemia could be prevented or cured by a diet supplemented with sources of vitamin B_2 (G) or some closely related substance. Liver extract was also an effective curative agent when administered orally but not when injected parenterally. The failure to improve with parenterally administered liver extract may be due, as Rhoads and Miller have suggested, to specie differences between man and the dog, mentioned also by others.[108] The effectiveness of

107. Wills, Lucy, and Billimoria, H. S.: Studies in Pernicious Anaemia of Pregnancy: V. Production of a Macrocytic Anaemia in Monkeys by Deficient Feeding, Indian J. M. Research **20**:391 (Oct.) 1932.

108. Strauss, M. B., and Castle, W. B.: Amount of Material Effective in Pernicious Anemia Present in Dog Liver, Proc. Soc. Exper. Biol. & Med. **31**: 360 (Dec.) 1933. Ivy, A. C.; Richter, O.; Meyer, A. F., and Greengard, H.: The Relation of Gastrectomy to Anemia: On the Presence of the Substances Effective in Pernicious Anemia in Canine Stomach and Liver, Am. J. Digest. Dis. & Nutrition **1**:116 (April) 1934.

autolyzed yeast and liver extracts administered by mouth, however, paralleled to a significant degree the results of the observations of Wills on the macrocytic anemia of pregnant women in India and of our observations in Puerto Rico on tropical sprue, as described later. It thus appears to be at least as reasonable to claim that there is a resemblance of the canine disorder produced by Rhoads and Miller to sprue as to pellagra.

In animals fed deficient diets there may also develop abnormal neurologic signs and pathologic lesions of the central nervous system resembling those sometimes seen in sprue. Cowgill [109] produced, by feeding dogs diets deficient in vitamin B, acute "polyneuritis" associated with so much spasticity as to suggest involvement of the central nervous system to Gildea, Kattwinkel and Castle.[110] With the same diet but with special attention to rendering the condition chronic these authors produced degenerative changes in the central nervous system suggestive of combined system disease. Subsequently, Zimmerman and his co-workers [111] were able to confirm these findings in dogs by using diets deficient only in vitamin B_2 (G). Crane-Lillie and Rhoads [112] found evidence of similar lesions in certain of the dogs studied by Rhoads and Miller.

Although the morphologic changes of the tongue, stomach and intestines of the animals which have been described suggest the possibility that physiologic disturbances known to be related to the production of macrocytic anemia accompany such lesions, it remained for Miller and Rhoads [113] to demonstrate this. In experiments on pigs these authors showed that the intrinsic factor of the gastric juice of normal animals could be caused to disappear by feeding them deficient diets similar to those used in their former experiments on dogs. This important fact became known when it was shown that the gastric juice of the

109. Cowgill, G. R.: A Contribution to the Study of the Relation Between Vitamin-B and the Nutrition of the Dog, Am. J. Physiol. **57**:420 (Oct.) 1921.

110. Gildea, E. F.; Kattwinkel, E. E., and Castle, W. B.: Experimental Combined System Disease, New England J. Med. **202**:523 (March 13) 1930.

111. Zimmerman, H. M., and Burack, Ethel: Studies on the Nervous System in Deficiency Diseases: II. Lesions Produced in the Dog by Diets Lacking the Water-Soluble, Heat-Stable Vitamin B_2 (G), J. Exper. Med. **59**:21 (Jan.) 1934.

112. Crane-Lillie, Margaret, and Rhoads, C. P.: Pathology of the Central Nervous System in Canine Black Tongue, Arch. Path. **18**:459 (Oct.) 1934.

113. Miller, D. K., and Rhoads, C. P.: The Experimental Production of Loss of Hematopoietic Element of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia, J. Clin. Investigation **14**:153 (March) 1935.

affected animals after incubation with autolyzed yeast was not effective in producing hematopoietic responses in patients with typical pernicious anemia. On the other hand, immediately thereafter in the same patients the gastric juice of normal pigs was active in promoting the formation of blood after incubation with autolyzed yeast, as was previously shown to be true of normal human gastric juice in similar observations on patients with pernicious anemia.[84] These experiments on pigs fed a deficient diet offer an explanation for the origin of the defect of the intrinsic factor observed in certain patients with sprue. The defective diets responsible for this result in the pigs produced also stomatitis, gastric anacidity, diarrhea, both macrocytic and microcytic anemia and in some instances neurologic disturbances.[113] Both varieties of anemia were associated with a megaloblastic type of hyperplasia of the bone marrow resembling that observed in sprue. As in sprue, the macrocytic anemia of the pigs and the neurologic disturbances responded to the intramuscular injection of liver extract. Finally, in contrast to the well known activity of normal pig liver, the livers of severely affected animals were shown not to contain substances hematopoietically active in patients with pernicious anemia. This demonstration parallels the observation which was made on the liver of a patient who died of sprue (case 81). Thus, the symptomatic, morphologic and physiologic features of the syndrome produced in pigs by defective diets are very similar to those of human sprue.

THE INFECTIOUS THEORY OF THE CAUSE OF SPRUE

In contrast to the facts outlined in support of the deficiency theory of the origin and later manifestations of sprue and its anemia, the infectious theory has little supporting evidence. Even if it is supposed that some type of infection of the alimentary tract is responsible for the lingual and gastro-intestinal manifestations of sprue, the problem of the origin of the anemia cannot be related to the infection without the interpolation of factors of deficiency. In vitro, at least, the addition of liver extract to yeast cultures on synthetic mediums has a remarkable accelerating action on growth. Since it is thus the reverse of an inhibiting agent, it is difficult to understand why the symptoms referable to the tongue and intestinal tract can be so readily abolished by an injection of liver extract if these disturbances are due to an infection.

In the opinion of Manson-Bahr and Willoughby,[36] much of the large amount of work on sprue during the past ten years from the bacteriologic point of view has only negative value. These authors, however, mentioned certain specific infections of the alimentary tract which may predispose to the development of the disease. Their analysis of the

previous illnesses of this type in the history of patients with sprue is as follows:

Previous Illnesses	Percentage
Diseases affecting the alimentary tract	40.5
Proved amebic dysentery Suspected amebic dysentery	32.0
Typhoid and paratyphoid	4.5
Hill diarrhea	2.0
Diarrhea: unclassified	1.0
Bacillary diarrhea	1.0

In this connection it is interesting to recall that diarrheal conditions are commonly associated with anemia [114] and deficiency diseases of other types [115] and may follow a wide variety of noninfectious intestinal lesions.[116] Mackie, Goré and Wadia [17] were unable to isolate bacteria recognized to be intestinal pathogens from the alimentary tract of 51 consecutive patients with sprue. In a later paragraph Manson-Bahr and Willoughby commented on the common observation that chronic alcoholism results in an acute or particularly intractable form of sprue. The relationship of dietary deficiency to "alcoholic" polyneuritis has recently been emphasized by Minot, Strauss and Cobb,[117] who among 57 patients with the latter condition observed pellagra in 14, edema associated with protein deficiency in several and hypochromic anemia in others. Complete gastric anacidity was observed in 21 of 43 patients appropriately examined. Spies and DeWolf [118] and Zimmerman, Cohen

114. Keefer, Huang and Yang.[90] Bennett, Hunter and Vaughan.[93]

115. Barnes, J. M.: Typical Pellagra Syndrome Developing in Patients with Chronic Ulcerative Colitis While Under Hospital Treatment, Ann. Clin. Med. **4**:552 (Jan.) 1926. Keefer, C. S., and Yang, C. S.: The Treatment for Secondary Anemia: A Study of the Results in One Hundred and Twenty-Six Cases, Arch. Int. Med. **48**:537 (Oct.) 1931. Jones, C. M.: Peripheral Complications of Ulcerative Colitis, M. Clin. North America **16**:919 (Jan.) 1933.

116. Urmy, T. V.; Ragle, B. H.; Allen, A. W., and Jones, C. M.: Beriberi Secondary to Short-Circuited Small Intestine, New England J. Med. **210**:251 (Feb. 1) 1934. Turner, R. H.: Pellagra Associated with Organic Disease of the Gastro-Intestinal Tract, Am. J. Trop. Med. **9**:129 (March) 1929. Strauss, M. B.: The Rôle of the Gastro-Intestinal Tract in Conditioning Deficiency Disease: Significance of Digestion and Absorption in Pernicious Anemia, Pellagra and "Alcoholic" and Other Forms of Polyneuritis, J. A. M. A. **103**:1 (July 7) 1934.

117. Minot, G. R.; Strauss, M. B., and Cobb, Stanley: "Alcoholic" Polyneuritis; Dietary Deficiency as a Factor in Its Production, New England J. Med. **208**:1244 (June 15) 1933.

118. Spies, T. D., and DeWolf, H. F.: Observations on the Etiological Relationship of Severe Alcoholism to Pellagra, Am. J. M. Sc. **186**:521 (Oct.) 1933.

and Gildea [119] have stated the etiologic importance of dietary deficiency in the frequent relationship of alcoholism to pellagra. Thus, by analogy with other deficiency diseases, dysentery, diverse intestinal disorders and chronic alcoholism are precisely the types of preceding illness which one would expect to find if defective nutrition is a predisposing cause of sprue. Hence, this type of evidence is quite as much in favor of dietary deficiency as of an infection as the predisposing cause of certain cases of sprue.

Kohlbrugge [9] originally suggested the etiologic rôle of yeastlike organisms in sprue. Space permits only a cursory review of the contradictory evidence on this subject. The results of cultural [120] and immunologic studies [121] have been extremely variable. Without a dietary regimen therapy by means of vaccines of these organisms has not been shown to be efficient to a significant degree.[122] Ashford, who did much to develop the hypothesis of yeast infection with which the strain of Monilia bearing his name was identified,[14] now considers sprue as an infection with Monilia psilosis made possible on a soil prepared by "nutritional unbalance." [16] He [81] found the scrapings of the tongue or the feces of 75 per cent of 225 patients with sprue positive for M. psilosis, whereas those of only 1.3 per cent of 223 patients with conditions not suggestive of sprue contained the organism. On the other hand, Mackie and Chitre [16a] found M. psilosis (Ashfordi) in only 40 per cent of cases of sprue in Bombay, and the organism was recovered with equal frequency from patients with other intestinal diseases, from healthy men and from animals. Monilias cultivated from patients with sprue by Ashford could not be distinguished by Nye, Zerfas and Cornwell [123] from yeastlike fungi isolated from the membrane or sputum of patients with typical thrush or from organisms frequently found in the human gastro-intestinal tract in a variety of diseases and occasionally in normal persons.

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119. Zimmerman, H. M.; Cohen, L. H., and Gildea, E. F.: Pellagra in Association with Chronic Alcoholism, Arch. Neurol. & Psychiat. **31**:290 (Feb.) 1934.

120. Bahr.[12] Ashford.[14] Mackie and Chitre.[16a]

121. Michel, Carl: A Study of Toxins and the Serological Reactions in Sprue, Am. J. M. Sc. **154**:177 (Aug.) 1917. Fairley, N. H., and Jasudasan, F.: An Investigation of the Value of the Complement Reaction in Sprue Utilizing Monilia Psilosis (Ashfordi) as Antigen, Indian J. M. Research **16**:861 (April) 1929.

122. Michel, Carl: On the Use of a Monilia Vaccine in the Treatment of Sprue, J. Infect. Dis. **22**:53, 1918. Ashford.[81]

123. Nye, R. N.; Zerfas, L. G., and Cornwell, M. A.: The Presence and Importance of Yeastlike Fungi in the Gastrointestinal Tract in Pernicious Anemia, in Other Diseases and in Normal Individuals, Am. J. M. Sc. **175**:153 (Feb.) 1928.

Fatal lesions can undoubtedly be produced in laboratory animals by the intravenous [124] and intraperitoneal [125] injection of yeastlike organisms isolated from the stools of patients with sprue. Nye, Zerfas and Cornwell,[126] however, believe that the Parasaccharomyces A group of fungi, regardless of their source, are pathogenic for rabbits if intravenously injected, the cause of death being invariably uremia. Other groups of yeastlike organisms isolated from the alimentary tract of man were found to be nonpathogenic on intravenous injection into rabbits. On the other hand, despite the reports of success by others,[127] these authors [126] found that the oral administration of fresh cultures of Parasaccharomyces A to guinea-pigs on a normal diet did not produce gastro-intestinal lesions. Nye and his co-workers [126] suggested that the importance of these organisms as infectious agents is in conditions of lowered resistance. After a study of the literature and as a result of experiments with monkeys, Mackie and Chitre [16b] concluded that sprue had not been produced in monkeys or other laboratory animals by means of organisms. Elsewhere [16a] they conceded only that infection with yeasts may contribute to the production of abdominal distention, intestinal flatulence and frothy stools in sprue.

Our few observations on this controversial subject bear out the negative conclusions. Systematic cultures of the stools of patients with sprue were made, through the cooperation of Dr. Amerigo Pomales, on Sabouraud's medium. The stools of 28 of the 56 patients so examined were found to contain yeastlike fungi on one or more occasions. A parallel series of cultures on the stools of 46 patients with hookworm infection and hyprochromic anemia yielded positive results on one or more occasions for only 13 patients. Of 15 patients with sprue and gastric anacidity, 11 had positive cultures for yeastlike organisms. This higher incidence of positive cultures in achylic subjects bears out the observations of Nye and his associates.[123] On the contrary, of 6 patients with hookworm infection and gastric anacidity, only 1 had yeasts in the stool. The results of the observations for individual patients are given in table 1.

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124. (*a*) Ashford, B. K.: Studies in Moniliasis of the Digestive Tract in Porto Rico, Am. J. M. Sc. **150**:680 (Nov.) 1915. (*b*) Smith, L. W.: The Rôle of Monilia Psilosis (Ashfordi) in Experimental Sprue Including Mycologic Observations on Twenty-One Strains of Monilia, J A. M. A. **83**:1549 (Nov. 15) 1924.

125. Smith.[124b] Mackie and Chitre.[16a]

126. Nye, R. N.; Zerfas, L. G., and Cornwell, M. A.: The Pathogenicity of Yeastlike Fungi Isolated from the Human Gastrointestinal Tract, Am. J. M. Sc. **178**:515 (Oct.) 1929.

127. Browne, D. C.: The Effects Produced in the Rabbit by Feeding Cultures of Monilia Psilosis, Proc. Soc. Exper. Biol. & Med. **24**:873 (June) 1927. Footnote 124.

The reported experiments on the pathogenicity of yeastlike organisms in animals were not sufficiently convincing to suggest danger in an assay on man. Accordingly, strains were isolated from the stools of 7 patients with severe sprue and were grown in dextrose broth for forty-eight hours. After the flasks were shaken, 100 cc. of the turbid contents was ingested three times daily for ten days by 2 normal subjects who had resided in Puerto Rico for six months. No symptoms were produced immediately or subsequently. In a patient with mild sprue and lingual and intestinal symptoms similar doses of the broth cultures were not observed to have any objective effect on the symptoms and signs already present. These observations at least offer no additional support to the idea that sprue is dependent on the presence of yeastlike organisms.

OBSERVATIONS CONCERNING THE TREATMENT OF SPRUE

The practice of prescribing a diet for any condition with gastro-intestinal symptoms is almost axiomatic in the lay and medical minds. To this principle the treatment of sprue with a dietary regimen including meat, milk or fruit has not been an exception. Benefit has also been ascribed to liver soup since its introduction by Sir Patrick Manson [35] in 1883. Nevertheless, the recent emphasis placed on intensive feeding of liver and liver extract in pernicious anemia has been carried over to the treatment of sprue largely as a method of combating the anemia.[128] Thus, although the oral administration of certain liver extracts [129] and stomach preparations [70] has been noted to produce hematopoietic effects in cases of sprue, some type of diet has usually been prescribed for the control of the diarrhea. The benefit to be derived from liver therapy in pernicious anemia is, however, not confined to the effect on the blood. Liver extract also affects favorably the lingual, gastro-intestinal and neurologic manifestations. As yet, little attention seems to have been paid to similar possibilities in the treatment of sprue. Recently Manson-Bahr and Willoughly [36] wrote: "The cure of sprue depends upon the administration of a nutritious and easily assimilable diet with the addition of protein and liver in order to stimulate the haemopoietic functions of the bone marrow."

EFFECT OF LIVER EXTRACTS ON THE LINGUAL AND GASTRO-INTESTINAL SYMPTOMS

Our investigations indicate a most regular and striking action of certain liver extracts effective in pernicious anemia on the lingual and gastro-intestinal symptoms of sprue. Since the patients were maintained

128. Ashford.[24] Manson-Bahr and Willoughby.[36]
129. Bloomfield and Wyckoff.[22] Suárez.[25a]

on a basal diet high in carbohydrate, containing no meat, eggs or fruit and very little milk, it is possible clearly to evaluate the effectiveness of the liver extract therapy. On the other hand, it is difficult to present graphically the evidence of improvement of the symptomatology in this direction in a quantitative fashion, as is possible in showing the improvement of the blood values. No particular observations of the effect of diets usually prescribed for sprue were made except from the point of view of the hematopoietic effects. Many of the patients treated with liver extract had, however, been maintained in the past on special diets or were actually adhering to diets at the time of admission to the hospital with severe symptoms and marked anemia. In some of these patients orally administered liver extract was effective in controlling lingual and gastro-intestinal symptoms, but the majority of the patients were not remarkably improved until treatment by the parenteral route was instituted. The usual initial dosage was the amount of liver extract derived from 50 or 100 Gm. of liver given by weekly injections or the amount derived from 10 Gm. of liver injected daily. Under this therapy lingual symptoms were invariably entirely relieved within a week, and diarrhea was usually greatly diminished or even abolished within a similar time. The epigastric distress and flatulence were correspondingly improved. Within two weeks the stools were usually formed. Occasionally the relief of vomiting or of profuse diarrhea was effected within twenty-four hours. At the same time the sense of well-being and the appetite were rapidly regained, and weight and strength were gradually augmented. These effects parallel the dramatic clinical results observed in the remission in pernicious anemia produced by adequate liver extract therapy. Nevertheless, subsequent experience [130] indicated that in a few cases of sprue larger injections of liver extract are necessary to produce initial improvement in the diarrhea, especially when the condition is of long standing. The statement that the successful treatment of pernicious anemia with liver extract depends on giving doses of the material adequate for the particular patient [131] holds equally in the treatment of sprue. During a continued experience with sprue since these observations were made, a special diet has been prescribed in few instances. In such cases it is possible that the initial daily administration of large amounts of liver extract intravenously, as was done in other instances of resistance to therapy,[130] would have controlled the situation without diet. After the initial improvement it has usually been found possible to maintain

130. Rhoads, C. P., and Miller, D. K.: Intensive Liver Extract Therapy of Sprue, J. A. M. A. **103**:387 (Aug. 11) 1934.

131. Minot, G. R., and Castle, W. B.: The Adequate Treatment of Anemia, Ann. Int. Med. **5**:159 (Aug.) 1931.

the patient free from sore tongue and diarrhea by injections at weekly intervals of liver extract derived from 50 to 100 Gm. of liver. In several instances the omission of liver extract therapy for a period of two weeks was sufficient to produce a recrudescence of sore tongue and looseness of the bowels, which were promptly abolished by the resumption of regular therapy. As in cases of pernicious anemia, the needs of the individual patients vary greatly, especially with oral therapy with liver extract. This variability in cases of sprue is even more prominent, probably because of the greater incidence of intestinal impermeability. Improvement from therapy with orally administered liver extract [23] or stomach preparations [70] can undoubtedly be obtained in certain cases. The use of diets containing sources of the extrinsic factor (meat, eggs) or the use of autolyzed yeast will probably not be beneficial unless the intrinsic factor is present in the gastric contents and unless intestinal absorption is adequate. Therefore, both for economic and for medical reasons the parenteral administration of liver extracts is the method of choice, certainly in patients in severe relapse. It is obvious that if irreversible anatomic changes in the intestines have occurred as a result of the chronicity or complications of sprue, the symptoms in the alimentary tract may not be entirely relieved. The extreme of this situation is probably illustrated by the persistent diarrhea and subsequent death of patient 57, in spite of an excellent hematopoietic response. With the availability of effective liver extracts for parenteral use we believe that the fundamental element in the treatment of the lingual and gastro-intestinal features of sprue is no longer a special diet but persistence in the administration of the amount of liver extract adequate for the particular patient.

TREATMENT OF THE ANEMIA, ESPECIALLY WITH PARENTERALLY ADMINISTERED LIVER EXTRACT

The treatment of the anemia of certain patients with sprue by diets containing meat and milk has become well recognized.[132] The relatively slight hematopoietic effects of the daily addition of 300 Gm. of meat and 1,500 cc. of milk to the basal diet of 9 patients have been discussed, and the results have been set forth in table 5. From the evidence it is seen that this mode of therapy will be hematopoietically effective only when the intrinsic factor is present in the gastric contents and absorption from the intestinal tract is adequate. It is thus evident, as others have found, that such diets cannot be expected to produce significant effects on the blood with regularity. In subsequent periods of observation on 7 of these 9 patients liver extract was administered both orally and parenterally. The details of these observations are given

132. Ashford.[28] Manson.[35] Manson-Bahr and Willoughby.[36]

TABLE 11.—*Results of Parenteral Administration of Liver*

Days	L. E. △ 10 l.m. Daily Case 6			L. E. △ 100 l.m. Every 10 Days Case 8			L. E. △ 10 l.m. Daily Case 16			L. E. △ 10 l.m. Daily Case 33			L. E. △ 10 l.m. Daily Case 36			L. E. △ 100 l.m. Once Case 43			L. E. △ 100 l.m. Every 10 Days Case 51		
	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent
0	1.30	33	1.4	0.72	23	6.0	1.23	31	1.4	2.30	48	2.8	0.69	21	0.4	0.55	17	0.6	0.72	13	2.2
2	1.27	36	1.0	0.81	25	6.4	1.31	29	1.0	1.68	45	1.4	0.89	25	0.2	0.65	18	...	0.94	16	4.4
4	1.17	40	2.8	1.16	32	39.4	1.53	35	1.4	....	..	1.4	0.90	23	0.4	0.66	18	1.0	0.89	19	21.2
6	1.54	47	10.8	1.52	35	**47.6**	1.49	31	5.2	1.58	48	4.4	0.87	26	6.0	0.56	23	**17.0**	1.13	25	**38.0**
8	1.72	47	**12.0**	1.88	41	19.4	1.82	39	12.0	1.66	52	**11.0**	1.14	31	**12.6**	0.80	25	14.8	1.45	31	6.8
10	2.06	50	4.4	....	..	...	1.86	40	**15.4**	1.95	50	8.0	1.13	37	10.0	0.79	25	9.2	1.71	35	5.6
12	2.15	53	2.2	1.90	40	4.8	2.20	40	8.4	....	..	...	1.44	39	3.6	0.79	26	5.4	1.81	36	7.6
14				....	..	...	2.37	47	7.0	2.08	57	...				1.06	27	4.8	2.02	44	12.0
16	....	..	...	2.14	46	7.8	2.43	48	2.4	2.12	59	...	....	..	...	0.72	26	9.0	2.48	44	17.4
18	....	..	...	....	..	...	**2.10**	**44**	**2.0**	....	..	...	....	..	...	1.23	30	7.0	2.83	53	5.6
20	....	..	...	3.07	61	5.2	**2.11**	**43**	**4.2**	2.73	65	...	....	..	...	1.50	34	8.0	2.72	55	4.8
22	....	..	...	....	..	...	**2.25**	**42**	**5.2**	....	..	...	....	..	...	1.65	33	6.0	2.96	60	4.2
24	....	..	...	....	..	...	**2.30**	**43**	**3.2**	....	..	...	....	..	...	**1.45**	**35**	6.6	....	..	...
26	....	..	...	....	..	...	1.93	**40**	**3.0**	....	..	...	....	..	...	1.65	35	3.8	....	..	...
28	....	..	...	3.76	74	...	**2.45**	43	**4.2**	3.12	74	...	....	..	...	**1.71**	35	4.6	2.96	59	3.4
Weeks																					
5	....	..	...	3.66	68	1.0	....	..	...	3.23	70	...	....	..	...	2.24	37	2.0	3.98	73	2.0
6	....	..	...	3.79	76	1.6	....	..	...	3.06	72	...	....	..	...				4.00	67	2.2
7	....	..	...	3.84	76	...	....	..	...	3.27	78	1.0	....	..	...	....	..	...	5.02	70	1.6
8	....	..	...	3.70	79	...	....	..	...	3.00	72	...	....	..	...	....	..	...	5.11	73	...
9	....	..	...	3.95	80	...	....	..	...	3.75	73	...	....	..	...	....	..	...	....	..	...
10	....	..	...	3.84	86	...	....	..	...	3.27	76	...	....	..	...	....	..	...	5.25	83	...

in table 5, and others are shown in tables 4 and 6. In certain patients the orally administered liver extract produced a rise in the reticulocyte count, but in other patients such a response first appeared or was repeated after the liver extract was administered parenterally. Since the publication of the preliminary report [27] of these studies, confirmatory results of the greater hematopoietic effects of parenterally administered liver extracts in cases of sprue have been made by Rogers and Cooke,[133] van der Scheer [134] and others.

The details of many observations on the effect of parenterally administered liver extract are shown in tables 4, 5, 6 and 11. An inspection of the data in table 12 for the highest percentage of reticulocytes obtained in each of 17 patients from the daily oral administration of liver extract derived from 300 Gm. of liver shows clearly that the responses, except in case 53, were less than would be expected from comparable therapy in similar patients with pernicious anemia. In 3 additional patients (cases 78, 90 and 92) the daily oral administration

133. Rogers, Leonard, and Cooke, W. E.: Resistant Sprue Anaemia Yielding to Intravenous Liver Extract, Brit. M. J. **1**:272 (Feb. 13) 1932.

134. van der Scheer, A.: Parenterale levertoediening bij tropische spruw, Nederl. tijdschr. v. geneesk. **77**:163 (Jan. 14) 1933.

L. E. △ 100 I.m. Every 10 Days Case 57			L. E. △ 50 I.m. Daily Case 64			L. E. △ 50 I.m. Daily Case 65			L. E. △ 10 I.m. Daily Case 71			L. E. △ 100 I.m. Every 7 Days Case 73			L. E. △ 10 I.m. Daily Case 74			L. E. △ 100 I.m. Every 10 Days Case 75		
Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent
0.75	25	6.6	0.60	18	0.6	0.68	17	3.8	2.26	60	4.0	1.33	36	2.0	1.23	35	1.0	0.79	23	2.4
0.76	27	10.4	0.65	18	0.4	0.64	19	4.0	1.89	54	0.1	1.29	35	2.4	1.02	32	2.8	0.69	19	2.0
0.88	27	16.0	0.69	18	9.0	0.88	27	10.0	1.72	53	1.8	1.28	37	4.6	1.05	34	9.2	0.66	21	13.2
1.04	36	33.8	0.88	23	21.2	1.03	26	**17.2**	1.95	55	4.8	2.10	45	**17.4**	1.22	39	**26.8**	0.78	24	**35.8**
1.22	35	**40.8**	1.26	28	**26.6**	1.42	30	7.6	2.11	60	**14.8**	2.20	51	12.2	1.75	42	12.0	1.40	29	21.6
1.44	39	8.0	1.58	40	7.0	1.55	29	4.6	2.32	62	10.6	2.29	48	5.4	2.10	50	3.8	1.53	35	8.4
1.41	36	9.2							2.45	61	3.6	2.36	55	4.8	2.08	50	6.2	1.57	35	9.0
1.63	35	10.2	....	..	...	....	..	...	L. E. △ 100 Every 7 Days			2.71	58	3.6	2.10	54	2.6	1.83	40	3.4
1.79	43	4.8	....	..	...	....	..	...	2.46	65	5.0	....	..	...	2.56	57	2.2	1.75	40	3.2
2.00	42	3.4	....	..	...	....	..	...	....	..	...	....	..	...	2.68	59	2.6	....	..	...
2.02	39	4.6	....	..	...	....	..	...	2.50	63	5.4	....	..	...	....	..	...	....	..	...
2.20	46	4.2	....	..	...	....	..	...	....	..	...	2.69	60	1.4	2.61	65	2.4	....	..	...
....	..	...	....	..	...	....	..	...	2.64	66	2.0	....	..	...	....	..	...	1.89	49	3.6
....	..	...	....	..	...	....	..	...	....	..	...	....	..	...	3.00	69	1.2	....	..	...
2.06	42	4.8	....	..	...	....	..	...	2.66	72	2.0	3.15	67	...	....	..	...	....	..	...
2.36	44	2.4	....	..	...	....	..	...	3.04	73	2.4	3.62	73	0.8	3.59	75	0.8	2.19	53	2.6
2.33	43	...	....	..	...	....	..	...	3.74	79	1.4	4.02	76	0.6	3.70	81	0.6	2.69	55	2.0
2.58	43	...	....	..	...	....	..	...	3.20	76	2.4	3.69	72	...	....	..	...	2.95	51	...
2.52	42	...	....	..	...	....	..	...	2.97	78	2.6				4.26	86	...	2.78	55	...
			....	..	...	....	..	...	3.35	80	1.8	....	..	...	....	..	...			
....	..	...	....	..	...	....	..	...	3.81	82	...	....	..	...	4.30	87	...	....	..	...

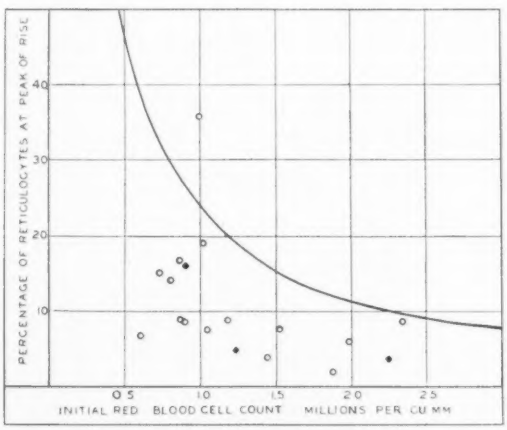

Chart 4.—The individual reticulocyte responses of 15 patients with sprue given daily by mouth liver extract derived from 300 Gm. of liver (circles), and the response of 3 patients with sprue given daily by mouth liver extract derived from 600 Gm. of liver (diamonds). The curved line indicates the average reticulocyte response expected in similarly anemic patients with pernicious anemia from the daily oral administration of liver extract derived from 300 Gm. of liver. Note that in only 1 patient with sprue was the expected response exceeded and that in most instances the responses were distinctly less than in pernicious anemia.

of liver extract derived from 600 Gm. of liver also gave distinctly submaximal reticulocyte responses. The percentage of reticulocytes at the peak of their rise for each of these 20 patients is plotted in chart 4 against the initial red blood cell count. The curved line in chart 4 is derived from the data of Minot and his associates [33a] and represents the average response of similar patients with pernicious anemia given daily about 230 Gm. of liver, which is approximately equivalent in potency to liver extract derived from 300 Gm. of liver. Since oral therapy was

TABLE 12.—*Response of the Reticulocytes and Increase of Red Blood Cells Resulting from Therapy with Liver Extract Administered by Mouth*

Case	Initial Therapy, Liver Extract	Maximal Reticulocyte Percentage		Red Blood Cells, Millions per Cu. Mm. at 10 Day Intervals				
		Expected	Observed	0 Days	10 Days	20 Days	30 Days	40 Days
4	△300 d.*	..	....	2.26	2.10	2.56	....	....
10	△300 d.	10	8.4	2.34	2.62	....	....	....
15	△300 d.	15	7.2	1.52	2.00	....	....	....
27	△300 d.	12	5.6	1.96	2.38	2.80	3.00	3.06
32	△300 d.	23	7.4	1.04	1.18	1.47	....	....
40	△300 d.	16	3.8	1.45	1.76	....	....	....
44	△300 d.	25	9.2	0.90	0.91	....	....	....
49	△300 d.	43	6.6	0.62	0.76	....	....	....
53	△300 d.	24	35.8	1.00	1.24	1.91	2.05	....
54	△300 d.	26	8.4	0.89	0.86	....	....	....
55	△300 d.	20	8.8	1.17	1.28	1.63	....	....
61	△300 d.	35	15.0	0.73	0.87	....	....	....
62	△300 d.	..	....	2.22	2.37	....	....	....
68	△300 d.	13	1.8	1.88	1.93	....	....	....
72	△300 d.	27	16.4	0.87	1.25	1.46	....	....
78	△600 d.	44	16.0	0.90	1.47	....	....	....
82	△300 d.	29	14.0	0.81	0.92	....	....	....
83	△300 d.	23	19.0	1.02	1.34	....	....	....
90	△600 d.	17	3.6	2.25	2.24	....	....	....
92	△600 d.	33	4.6	1.24	1.00	....	....	....
Average number of red blood cells.....				1.35	1.52			

* △ (derived from), 300 (Gm. of liver), d. (daily).

changed to parenteral therapy after from ten to fourteen days for most of these patients, the data concerning increases in the red blood cell count are insufficient to justify conclusions. The average increase of red blood cells in the first ten days of therapy for these 20 patients was, however, only 170,000 per cubic millimeter, in contrast with an expected increase of about 600,000 for comparably anemic patients with pernicious anemia (chart 6).

In table 13 are shown data derived from observations on 18 patients given daily by intramuscular injection liver extract derived from 10 Gm. of liver, as well as data on 12 patients given the same liver extract

derived usually from 100 Gm. of liver at intervals of seven or ten days. Another patient (case 64) received the extract derived from 50 Gm. of liver daily by injection. The details of the observations on certain patients are shown in tables 4, 5, 6, 10 and 11. Table 13 shows the reticulocyte responses obtained in each patient, as well as the response to be expected in similar patients with pernicious anemia for each method of administration. In chart 5 the maximal percentage of the reticulocytes attained in each patient is plotted against the initial red blood cell count. The lower curve in the chart is derived from the data of Minot and his associates [33a, b] for the average reticulocyte response in pernicious anemia to the daily oral administration of liver extract derived from 600 Gm. of liver. These values, given by Bethell and Goldhamer,[33c] correspond to the average response to be expected from the daily intramuscular injection of liver extract derived from 10 Gm. of liver, according to the observations of Strauss, Taylor and Castle.[89] The upper curve in chart 5, according to Bethell and Goldhamer, corresponds to the average expected response of the reticulocytes in pernicious anemia resulting from a single intravenous injection of liver extract derived from 100 Gm. of liver. The individual responses plotted in chart 5 show that the reticulocyte response expected in pernicious anemia was not attained by either method of parenteral administration in any patient with sprue. In many instances the responses were greatly inferior to those expected in comparably anemic patients with pernicious anemia.

In table 13 are also shown the red blood cell values of each patient plotted at successive ten day intervals after the beginning of parenteral liver extract therapy. The bold face figures indicate the periods during which certain patients were also receiving iron. At the bottom of the table are shown the average red blood cell counts for the whole group at ten day intervals.

These average red blood cell counts are plotted against days in chart 6 in the solid line with solid dots. From the information given by Isaacs, Sturgis, Goldhamer and Bethell,[85b] a solid line with open circles connecting four points on the chart has been drawn to indicate the increases of the red blood cell count observed by these authors in 10 cases of pernicious anemia with an average initial red blood cell count of 1,420,000 per cubic millimeter. Their patients were given weekly intravenous injections of the extract derived from 100 to 125 Gm. of liver. The average weekly increase during the first two weeks was 573,000 per cubic millimeter. In fifty days the average red blood cell count had increased to 4,290,000 per cubic millimeter. The broken line extending over a period of thirty days represents the results of the

observations of Minot and his co-workers [33b] on 24 patients with uncomplicated pernicious anemia given daily by mouth liver extract derived from 500 or 600 Gm. of liver. The average initial red blood cell count of these patients was 1,200,000 per cubic millimeter. At the end of thirty days it had reached an average of 3,800,000 per cubic millimeter. Finally, the broken line with circles represents the average increase of red

TABLE 13.—*Response of the Reticulocytes and Increase of Red Blood Cells Resulting from Therapy with Liver Extract Administered Parenterally and from the Addition of Orally Administered Ferric Ammonium Citrate (6 Gm. Daily)*

Case	Initial Therapy Liver Extract	Maximal Reticulocyte Percentage		Red Blood Cells, Millions per Cu. Mm. at 10 Day Intervals									
		Expected	Observed	0 Da.	10 Da.	20 Da.	30 Da.	40 Da.	50 Da.	60 Da.	70 Da.	80 Da.	90 Da.
4	△ 10 d.*	10.0	5.6	2.34	2.68	2.58	2.85	3.10	**3.36**	**3.60**	**3.95**	**4.10**	4.18
5	△ 10 d.	17.7	7.2	1.76	2.83	2.96	....	....	....	....	....	....	....
6	△ 10 d.	26.5	12.0	1.30	2.06	**2.30**	**2.90**	**3.54**	**3.95**	**4.00**	**4.13**	**4.33**	4.50
8	△ 100	54.1	47.6	0.80	1.90	3.07	3.76	3.66	3.79	3.84	3.70	3.95	4.07
12	△ 10 d.	8.5	3.0	2.49	2.53	2.82	3.44	....	....	....	....	....	....
14	△ 10 d.	9.0	6.6	2.46	2.65	....	....	....	....	....	....	....	....
16	△ 10 d.	26.3	13.2	1.31	2.20	2.25	2.49	**3.24**	....	....	....	....	....
19	△ 10 d.	27.0	15.8	1.28	1.50	1.58	....	....	....	....	....	....	....
30	△ 100 w.*	38.5	22.2	1.31	2.01	2.60	2.80	2.60	3.30	3.40	**3.76**	**3.68**	3.85
31	△ 10 d.	28.7	9.8	1.21	1.32	2.55	3.13	**3.63**	**3.60**	**4.18**	**4.33**	**4.60**	....
33	△ 10 d.	22.7	11.0	1.48	1.95	2.73	3.19	3.12	3.22	3.53	3.20	3.36	3.51
36	△ 10 d.	38.0	12.6	0.90	1.13	1.22	1.22	1.20	1.71	1.90	2.62	2.60	....
37	△ 10 d.	18.1	5.9	1.74	1.90	2.67	3.00	....	....	....	....	....	....
40	△ 10 d.	18.7	15.0	1.70	2.50	3.08	3.38	3.78	....	....	....	....	....
43	△ 100	61.8	17.0	0.60	0.79	1.50	2.13	2.68	3.26	**3.36**	....	....	....
45	△ 10 d.	15.1	8.0	1.93	2.13	3.08	3.16	3.32	3.50	**3.67**	**3.88**	**3.94**	4.00
47	△ 10 d.	16.8	5.6	1.82	2.23	2.33	**2.42**	**2.81**	**3.20**	**3.28**	**3.80**	....	....
51	△ 100, 10 d.	57.8	38.0	0.70	1.45	2.83	2.96	3.98	4.90	5.13	5.18	5.22	5.26
57	△ 100, 10 d.	54.1	40.8	0.80	1.41	1.73	2.36	2.33	2.58	**3.03**	....	....	....
58	△ 100, 10 d.	17.5	5.8	2.34	2.85	2.87	....	....	....	....	....	....	....
59	△ 100, 10 d.	43.7	25.6	1.12	1.78	2.35	3.50	....	....	....	....	....	....
62	△ 100 w.	....	....	2.24	2.70	3.40	3.30	3.30	....	....	....	....	....
64	△ 50 d.	61.8	26.6	0.60	1.58	**2.01**	**2.30**	**2.63**	**2.90**	**2.76**	**3.42**	....	....
65	△ 100 w.	58.6	17.2	0.68	1.55	**2.84**	**3.43**	**3.70**	**4.32**	**4.24**	....	....	....
71	△ 10 d.	15.8	14.8	1.89	2.45	2.64	3.03	3.74	3.20	3.46	3.85	....	....
73	△ 100 w.	39.2	17.4	1.28	2.40	2.80	3.50	4.00	....	....	....	....	....
74	△ 100 w.	44.3	26.8	1.10	2.10	2.60	3.26	3.56	3.84	4.20	4.00	4.30	4.62
75	△ 100, 10 d.	54.1	35.8	0.80	1.53	1.88	2.30	2.50	2.95	2.90	**2.85**	**3.00**	3.20
79	△ 10 d.	27.8	9.2	1.25	1.55	1.91	2.36	2.76	3.18	....	....	....	....
86	△ 10 d.	17.7	12.6	1.76	1.71	**2.34**	3.17	....	....	....	....	....	....
88	△ 10 d.	23.9	13.8	1.42	2.09	2.14	**2.81**	**3.67**	....	....	....	....	....
90	△ 100, 10 d.	19.5	6.0	2.24	3.07	3.39	....	....	....	....	....	....	....
92	△ 100, 10 d.	47.4	29.8	1.00	1.95	3.20	3.35	3.87	3.85	4.13	4.45	....	....
Average number of red blood cells				1.44	2.01	2.36	2.91	3.20	3.40	3.59	3.80	3.92	4.13

* △ (derived from), 10 (Gm. of liver), d. (daily); w. (weekly.)
The bold face figures indicate the response after the addition of ferric ammonium citrate.

blood cells in 105 unselected patients with pernicious anemia observed by Minot and Murphy [26] who received a diet containing daily about 200 Gm. of cooked liver.

It is evident that the average increase of erythrocytes in these patients with sprue was less than in any of the groups of patients with pernicious anemia. Had the effect of therapy with liver extract on the anemia of the two diseases been comparable the increase of erythro-

cytes should have been about as rapid as that produced by the daily oral administration of liver extract derived from 500 or 600 Gm. of liver (broken line) and probably almost as rapid as that produced by the weekly injection of the extract derived from 100 Gm. of liver (solid line and circles). As a matter of fact, it was not even as rapid as the average increase of erythrocytes of patients with pernicious anemia in response to a diet containing 200 Gm. of liver daily (broken line and circles).

The smaller rises in the number of reticulocytes and the slower gains of the erythrocyte count in response to liver extract therapy obtained in the anemia of sprue as contrasted with those achieved in addisonian

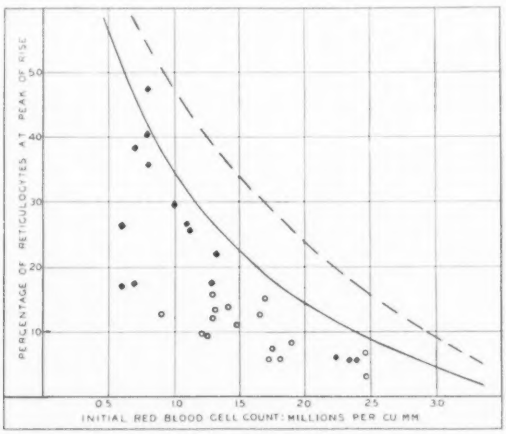

Chart 5.—The individual reticulocyte responses of 16 patients with sprue given daily by injection liver extract derived from 10 Gm. of liver (circles). The lower curve in the figure indicates the reticulocyte response to be expected from such therapy in equally anemic patients with pernicious anemia. The individual reticulocyte response of 15 patients with sprue given one or more injections of liver extract derived from 100 Gm. of liver at intervals of a week or ten days are indicated by the diamonds. The upper curve corresponds to the average reticulocyte response to be expected in equally anemic patients with pernicious anemia given by intravenous injection the extract derived from 100 Gm. of liver. Note that in no instance was a reticulocyte response attained in the patients with sprue comparable with those observed in patients with pernicious anemia.

pernicious anemia cannot be entirely explained by our observations. The possible influence of difficulty with the absorption of hematopoietic material may be partly responsible for the relatively slight effect of orally administered material on the production of reticulocytes. This explanation, however, cannot be considered pertinent when therapy is

administered parenterally. It is known that in certain patients with pernicious anemia a "double deficiency" exists in the sense that optimal formation of blood is not possible without the use of both liver extract and iron. Observations indicate that this is also true in certain patients with sprue. Initially in a few patients and in the later stages of the recovery of several of the patients, the effectiveness of iron was clearly demonstrated (table 11). The administration of both iron and liver extract from the beginning was not attempted; so it is not possible to state that the original response of the reticulocytes would have been enhanced by the combination. In the absence of such data it is possible only to speculate on the further evidence supplied by the morphology of the bone marrow. Certainly no patients were found to have a con-

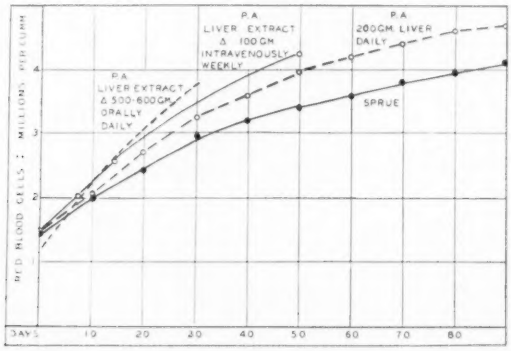

Chart 6.—The average increase of red blood cells in 33 patients with sprue with less than 2,500,000 red blood cells per cubic millimeter following parenteral therapy with liver extract in the dosage indicated in table 13. In those patients indicated in table 13, daily oral administration of 6 Gm. of ferric ammonium citrate was added. The solid line with dots indicates the results in the patients with sprue. The solid line with circles indicates the effect of the weekly intravenous injection of liver extract derived from 100 Gm. of liver on 10 patients with pernicious anemia and a comparable red cell count. The broken line, extending over a period of thirty days, indicates the average effect on 24 comparably anemic patients with pernicious anemia given daily by mouth liver extract derived from 500 to 600 Gm. of liver. The broken line with circles represents the average increase of red blood cells of 105 patients with pernicious anemia given daily about 200 Gm. of liver. Note that the average increase of red blood cells in patients with sprue was less than that in patients with pernicious anemia treated with liver or liver extract whether orally or parenterally administered.

dition in the normally active bone marrow suggesting the aplasia found in the long bones by others, nor were hematopoietic responses to the administration of liver extract lacking in any patient. It is, however, our impression that the extension of the hyperplastic marrow to the long bones in patients with sprue is not so marked or so regular as in

those with pernicious anemia. Thus, in pernicious anemia the larger amount of hyperplastic marrow available for activity after the administration of liver extract might explain the greater hematopoietic responses. The influence of infection is another factor which sometimes inhibits the response of patients with pernicious anemia to liver extract. It is hardly probable that infection sufficient to inhibit the response of the hematopoietic organs could have been present in every patient and not have been detected. The presence of yeastlike organisms in the intestinal tract was not constant in these patients, and from a survey of the work of others and of our work on this subject it is impossible to become convinced of their etiologic importance. What is certain is that in every patient not proved to have a complicating infection some degree of initial hematopoietic response to parenterally administered liver extracts effective in pernicious anemia was observed and that later progress could be accelerated in many patients by iron. Since this was accomplished without the use of the diets usually prescribed, it is clear that the use of special diets is not necessary for increasing the production of blood.

MISCELLANEOUS ASPECTS OF TREATMENT

In the observations made on 8 patients considered to have suggestive evidence of neurologic complications parenterally administered liver extract over several weeks gradually caused a decrease in the symptoms. The paresthesia became distinctly less or disappeared, and in 2 instances the gait was definitely improved. This slow improvement corresponds to that observed in patients with combined system disease and pernicious anemia.[135] In 1 patient with sprue, observed since this series of observations, two preceding attacks of profuse diarrhea associated with severe tetany with a lowered value for blood calcium had been relieved by therapy with calcium and viosterol. While this patient was under observation a moderate degree of tetany again developed, and the blood calcium was found to be 7.1 mg. per hundred cubic centimeters. Calcium lactate and viosterol again promptly abated the attack in spite of persistent diarrhea which was not checked until liver extract was given parenterally. Similar results were subsequently observed in another patient.

The progressive improvement of all aspects of these patients with sprue after the institution of therapy with parenterally administered liver extract has been described with many illustrations. Among the 92 patients there were, however, 4 deaths.

135. Ungley, C. C., and Suzman, M. M.: Subacute Combined Degeneration of the Cord: Symptomatology and Effects of Liver Therapy, Brain **52**:271 (Sept.) 1929. Minot and Murphy.[26]

Patient 57 was a 67 year old Puerto Rican woman who had suffered from sprue for two years. She had profuse diarrhea and showed great emaciation. She was adequately treated with liver extract by parenteral injection and subsequently with iron. An excellent hematopoietic response occurred, as shown in table 11. Nevertheless, the patient continued to have a low grade fever, her appetite did not improve, and the diarrhea was not controlled. Tuberculous enteritis was suspected but never proved. Autopsy was not performed.

In case 76 a 34 year old Puerto Rican had suffered from sprue for ten months. Except for severe anemia he appeared to be in good condition, with little diarrhea. Attempts to administer a diet containing meat resulted in vomiting, an increase of diarrhea and sudden collapse and rise of temperature. On the day before death liver extract derived from 100 Gm. of liver was given by intramuscular injection. Autopsy revealed observations typical of sprue and disclosed multiple small abscesses of the lungs.

In case 77, a 66 year old man had suffered from sprue for three months. He was moderately anemic and emaciated and complained of cough. Examination of the lungs gave negative results. After a month of therapy with orally administered liver extract derived from 300 Gm. of liver daily, the blood values were not improved. Because of increased cough, pain in the chest and fever he was admitted to the hospital. He was then given a single injection of liver extract derived from 100 Gm. of liver, from which no reticulocyte response occurred within ten days. As he was then not improved clinically he was given half that amount of liver extract by intravenous injection daily for four days without benefit before his death. Autopsy revealed observations typical of sprue and disclosed a single, large chronic abscess of the lung.

Patient 81 was a 62 year old Puerto Rican who had suffered from sprue for six years. He was moderately emaciated and severely anemic despite adherence to a diet for sprue. Oral therapy with autolyzed yeast was begun, but because of the patient's poor condition it was discontinued on the fourth day. A transfusion of 300 cc. of blood and a single intramuscular injection of liver extract derived from 100 Gm. of liver were given without improvement. The patient died the next day. Autopsy revealed observations typical of uncomplicated sprue.

Of the 4 patients who died, those in cases 57 and 77 were adequately treated with liver extract parenterally administered but probably had complications which were responsible for the fatal outcome. Patients 76 and 81 did not receive therapy for a sufficient length of time to regard the result as a failure of therapy with liver extract parenterally administered. In all the other patients treated parenterally with liver extract and, if necessary, with iron, clinical and hematologic improvement occurred. That the values for red blood cells and for hemoglobin were in some cases only slowly elevated is evidenced by the data already presented. In the majority of cases, however, the prompt relief of symptoms referable to the alimentary tract and the progressive increase of blood values were striking as soon as parenteral therapy with liver extract was instituted. This improvement, moreover, was produced in several instances when the failure of other methods of treatment was all too evident.

SUMMARY

The evidence for our belief that sprue is a deficiency disease closely related to addisonian pernicious anemia has been presented in detail.

The chief manifestations of both diseases consist in the disturbances of the tongue, stomach and intestines, the anemia and (rarely in sprue) the degenerative lesions of the spinal cord. These several organs are admittedly not all affected in each patient with either disease, but the characteristic manifestations of each disease are distinguishable largely by their differing intensity. In certain instances, however, it was beyond our clinical ability to decide whether the condition under observation in Puerto Rico was sprue or pernicious anemia. Especially was this true of the appearance of the tongue, the blood picture and the histologic changes in those regions of the bone marrow which were normally active.

Certain therapeutic agents relieve the lingual and gastro-intestinal manifestations, abolish the macrocytic anemia and improve the disturbances of the nervous system in both diseases. The parenteral administration of the liver fraction G of Cohn, Minot and their associates [21] invariably relieved the "inflammation" of the tongue, as in pernicious anemia. It produced characteristic hematopoietic responses in patients with macrocytic anemia, definite but not so great as in patients with pernicious anemia. Failure of the hematopoietic activity of this liver extract on oral administration in certain patients with sprue, which had been observed by others, was confirmed but was satisfactorily explained by the demonstration of the subsequent activity of the liver extract in the same patients on parenteral administration. Slow improvement of the paresthesia and ataxia of the few patients so affected resulted from therapy with liver extract parenterally administered, as in pernicious anemia.

These analogies led to the discovery of intimate resemblances between the two diseases in respect to a disturbance of a specific reaction leading in the normal person to the production of "liver extract." It was observed that the lingual and gastro-intestinal manifestations of incipient sprue could be abolished by the administration of beef muscle or of preparations of autolyzed yeast in certain patients. In other patients this could be accomplished only after the addition of normal human gastric juice. The failure of this reaction between a food (extrinsic) and a gastric (intrinsic) factor has been repeatedly demonstrated in addisonian pernicious anemia in relapse. The acid-containing gastric contents of 2 patients with fully developed sprue and macrocytic anemia, when examined by tests such as those given patients with pernicious anemia, showed a lack of the intrinsic factor. In a third patient with a short history of sprue and little

anemia, similar tests indicated the presence of the intrinsic factor in the acid-containing and pepsin-containing gastric juice. Thus, the failure of the reaction in patients with pernicious anemia, usually due to a lack of the intrinsic factor, was produced in certain patients with sprue in an identical manner. In other patients the failure of this reaction was due to a lack of the extrinsic factor. A further analogy with addisonian pernicious anemia was observed in the relative ineffectiveness of orally administered liver extract on the anemia of certain patients with sprue. The subsequent considerable activity of parenterally administered material in these same patients was considered to suggest, but not to establish beyond question, the presence of intestinal impermeability to hematopoietic substances.

Thus, the development of sprue and its macrocytic anemia was considered to be due in different patients to the variable participation of three causes: (1) a lack of a factor (extrinsic) in the diet associated with vitamin B_2 (G) in meat, eggs and whole cereal but not as yet identified as any fraction of the vitamin B complex; (2) a failure of the secretion of a factor (intrinsic) in the normal gastric juice presumably identical with the substance usually lacking in addisonian pernicious anemia in relapse, and (3) difficulty with the absorption of the products of this reaction from the intestinal tract. The influence of dietary defect, gastric anacidity and intestinal impermeability on the intake of iron is considered to have a bearing on the defective metabolism of iron and consequent hypochromic anemia of certain patients with sprue. The possibility of the increasing influence of intestinal impermeability in the more advanced disease was pointed out. Destruction of hematopoietic substances in the gastro-intestinal tract as well as defects of their utilization within the body are also theoretically important factors.

By analogy with pernicious anemia, as a result of defects of one or more of the foregoing mechanisms of deficiency, a deficiency of "liver extract" should exist in the bodies of the patients with sprue and macrocytic anemia. This fact was proved by the demonstration that the liver of a patient who died of sprue with severe macrocytic anemia did not contain detectable amounts of the "liver extract" hematopoietically active in pernicious anemia. The same observation has been made in cases of addisonian pernicious anemia and has been regarded as evidence of the nature of the internal deficiency in that condition.

Certain authors have observed that defective diets in animals lead to marked symptoms and pathologic findings in the tongue, stomach and intestinal tract. Such symptoms, together with macrocytic anemia responding to the oral administration of a liver extract

effective in pernicious anemia, have been produced in dogs by Rhoads and Miller. Similar anemia, responding to the oral administration of a source of the extrinsic factor (Marmite) or of liver extract, has been produced in monkeys by Wills. In both kinds of animals hyperplasia of the bone marrow of a megaloblastic type was produced. The diets causing these results were in both instances deficient in vitamin B_2 (G) or substances frequently associated with it. Symptoms and pathologic changes in the central nervous system resembling combined system disease have also been produced in dogs by diets deficient in vitamin B or some related substance. Thus, the major clinical features of sprue have been produced in animals with deficient diets and the manifestations abolished by substances known to be therapeutically effective in both sprue and pernicious anemia. The observations of Ashford as well as our analysis of the diets of patients with sprue clearly favor the possibility of the existence of dietary defects similar to those of the animals. Wills' animals were actually given diets based on those of patients suffering from tropical macrocytic anemia.

Since the administration of defective diets to animals may produce not only macrocytic anemia but also profound morphologic and physiologic derangements of the alimentary tract, a cause sufficient to account for the secretory and probably for the absorptive defects of the patient with sprue is exhibited. It is likely, therefore, that the influence of a deficiency of the extrinsic factor or some related substance may originally be responsible for diminishing the intrinsic factor secreted by the stomach, as was demonstrated by the observations of Miller and Rhoads [113] on pigs, or for producing other degenerative changes leading to intestinal impermeability. Thus, as has been pointed out elsewhere [62b] in relation to pernicious anemia, a vicious cycle would be created. The original effect of a defective diet would subsequently be enhanced by the development of the defects of the alimentary tract involved in the production of macrocytic anemia. The reversal of this cycle in pernicious anemia by effective treatment with liver extract has been demonstrated by the reappearance of the intrinsic factor formerly absent from the gastric juice.[62b] In pernicious anemia, however, aside from extirpation of the stomach or its destruction by cancer, the usual subtle process leading to a disappearance of the intrinsic factor has not been disclosed. In sprue the obvious dietary defects provide, by analogy with experiments on animals, a rational explanation of the subsequent defects of the specific functions of the alimentary tract demonstrated in patients. It would perhaps be well to borrow the information disclosed by a study of sprue and seek its application to the problems of pernicious anemia.

On the other hand, most investigators have been unable to reproduce in animals the clinical picture of sprue by the use of yeastlike organisms. The inconstancy of the finding of yeasts in the stools of patients with sprue, the lack of immunologic evidence for an etiologic relationship and the frequent occurrence of these organisms in the stools of patients lacking symptoms of sprue have been discussed. The negative effect on man of the oral administration of cultures of yeasts isolated from the stools of patients with active sprue was observed. The importance of dysentery, chronic alcoholism and noninfectious lesions of the alimentary tract in producing a variety of deficiency diseases has been reported. Thus, the predisposing influence of these conditions may be as logically interpreted on the basis of their effect on nutrition as on the basis of infection.

The alleged influence of a short residence in the tropics on the development of sprue, soon or late, remains a mystery. Nevertheless, if it results in the disease which we have observed a deficiency state must eventually be involved. We can only suggest the obligatory modification of the diet of the northern visitor, noted by Ashford, the deleterious effect of continued high temperature on the appetite which is commonly experienced and the decrease of gastric secretion which is demonstrable under these circumstances.[136] It is also possible that the occasional person who acquires sprue shortly after arrival in the tropics was already closer to "pernicious anemia" than he realized or was originally hastened into a deficiency state by the onset of some type of infectious dysentery.

The explanation of the etiology of sprue which we have advanced and in particular the analogies drawn between sprue and pernicious anemia will doubtless encounter many objections. In their respective territories the classic examples of each disease obviously differ in their clinical pictures. Yet these differences are scarcely greater than are the differences between the clinical picture of incipient sprue and that of the full-blown disease or between the aspect of a patient with severe combined system disease and little anemia and that of a patient with classic addisonian pernicious anemia. It has been our experience to observe patients who reported leaving the tropics with symptoms typical of sprue but who on examination a few weeks later in Boston presented no obvious differences from pernicious anemia. The explanation of the varied manifestations of other deficiency diseases in man is hardly more satisfactory. From the practical point of view of

136. Bogendörfer, L., and Sell, A. R.: Ueber die Wirkung von äusseren Temperaturreizen auf die Sekretionstätigkeit des Magens, Deutsches Arch. f. klin. Med. **169**:166, 1930.

therapy, however, these distinctions are of purely academic interest. That sprue is a close relative of pernicious anemia in its chief manifestations can scarcely be doubted by one who has had occasion to observe the remarkable benefit resulting from the parenteral administration of liver extract to severely sick patients with both diseases.

As a result of our observations on these patients and on others subsequently studied we emphasize the primary importance of the adequate treatment of the patient with sprue with parenterally administered liver extract as a method not only of combating the anemia but of controlling the lingual and gastro-intestinal manifestations of the disease. Repeated experience has shown that when therapy including diet or orally administered liver extract has failed the results of parenterally administered liver extract may be brilliant. Moreover, partial failure with the use of parenterally administered liver extract in the hands of others have been turned into success by the use of larger dosage and through greater persistence.[118] The intravenous route in such patients has undoubted advantages for the daily administration of the extract derived from as much as 100 Gm. of liver, which may initially be necessary. The accessory value of iron in the relief of the anemia has been pointed out. The tabulated evidence is largely confined to the hematopoietic results, since it is not possible to present the evidence of improvement of the lingual and intestinal symptoms in a similar quantitative manner. In no type of disease are the results of adequate treatment so gratifying and so uniformly successful as in those conditions now recognized as related directly or indirectly to defects of the diet or its subsequent utilization by the patient. A share in such improvement is possible, in our opinion, for practically all sufferers from sprue provided therapy with liver extract is adequate.

CONCLUSIONS

The following morphologic and physiologic observations indicate that sprue is fundamentally a deficiency disease closely related to addisonian pernicious anemia.

MORPHOLOGIC OBSERVATIONS

1. Involvement of the tongue and alimentary tract, the blood and (rarely) the nervous system was observed in sprue, which thus selects the same systems of the body as does pernicious anemia. Although the characteristic frequency and intensity of the manifestations in these systems are typically different in the two diseases, the condition in certain patients with sprue was found to be indistinguishable clinically from that in patients with pernicious anemia.

2. The macrocytic anemia of sprue closely resembled that of pernicious anemia.

3. The megaloblastic proliferation of the normally active bone marrow, found in patients with sprue and macrocytic anemia, resembled closely that of pernicious anemia.

PHYSIOLOGIC OBSERVATIONS

1. The manifestations of the tongue and alimentary tract as well as the macrocytic anemia of sprue were invariably benefited by adequate doses of a liver extract given by parenteral injection and known to be effective in pernicious anemia.

2. Sources of the extrinsic factor, hematopoietically active in persons with pernicious anemia only after contact with normal human gastric juice, were effective alone in certain patients with sprue. In other patients the extrinsic factor was effective on the lingual symptoms or on the macrocytic anemia of sprue only when administered with normal human gastric juice. The dietary histories of many patients with sprue suggested a deficiency of certain sources of the extrinsic factor, such as meat, eggs and whole cereals.

3. The usual absence of the intrinsic factor from the gastric contents of patients with pernicious anemia was paralleled in certain patients with sprue. In other patients with sprue the intrinsic factor was present in the gastric contents.

4. Liver extracts administered orally, as in certain patients with pernicious anemia, were relatively ineffective in many patients with sprue, but on parenteral administration they favorably affected the formation of blood.

5. The liver of a patient who died of sprue and macrocytic anemia, like that of patients with pernicious anemia in relapse, was found to contain no detectable amount of liver extract.

6. As in certain patients with pernicious anemia, an additional hematopoietic response was produced by the administration of iron.

GENERAL CONCLUSIONS

It is believed, therefore, that in sprue, as in pernicious anemia, there is involved the failure of a reaction between an extrinsic factor in the diet, associated in several substances with vitamin B_2 (G), and an intrinsic factor, present in the gastric contents of the normal person. In addition, difficulty with the absorption of substances from the intestinal tract resulting from this hematopoietic reaction is probably involved in certain instances of both diseases. In different patients with sprue the relative importance of these mechanisms is variable. Sprue

with macrocytic anemia thus arises from the variable participation of three defects: of the extrinsic factor, of the intrinsic factor and of absorption. Dietary deficiency of iron, gastric anacidity and intestinal impermeability may also decrease the normal intake of iron.

By means of diets deficient in sources of the extrinsic factor or closely related substances, lingual and gastro-intestinal lesions, macrocytic anemia with megaloblastic bone marrow and degenerative lesions of the spinal cord have been produced in animals. These manifestations can be abolished by means of liver extract or the extrinsic factor. The gastric secretion of pigs fed appropriately defective diets loses its normal content of the intrinsic factor, and the liver becomes deficient in substances normally present and capable of producing increased formation of blood in cases of pernicious anemia. Therefore, the disease picture in animals may reasonably be regarded as analogous to that in patients with sprue. Appropriate dietary defects in man may likewise initiate the physiologic disturbances of the alimentary tract subsequently involved in the production of sprue.

The evidence for the primary etiologic relationship of yeastlike organisms to sprue is not convincingly supported by observations on animals or on man.

The administration of adequate doses of liver extracts effective in pernicious anemia, especially by parenteral injection, is fundamental in the treatment of sprue and its macrocytic anemia. The accessory use of iron is indicated for certain patients.

It is emphasized that adequate doses of liver extract are as important in controlling the manifestations of the alimentary tract as in promoting the formation of blood in cases of sprue.

CLINICAL EXPERIENCE WITH A DERIVATIVE OF SQUILL

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This study of scillonin includes observations on 104 patients to whom the drug was given for cardiac decompensation. To these 104 patients 119 courses were given. The records for 85 patients are sufficiently complete to be used in compilations; to these patients 97 courses were given. Most of the subjects were observed at the Cook County Hospital, although some were seen at the Evanston, Wesley Memorial and Passavant Memorial Hospitals and the dispensary of Northwestern University Medical School. The drug herein reported on is a derivative of squill supplied to us in the form of tablets of 0.5 and 0.25 mg. The tablets of 0.25 mg. were assayed by Dr. H. B. Van Dyke of the University of Chicago. He reported that each tablet was equal to 1.15 of a cat unit; 1 cat unit was approximately 0.21 mg. This figure is the true average lethal dose to within 19.4 per cent. Each tablet of 0.25 mg. was approximately equivalent to 0.09 mg. of ouabain or to 79 mg. of international standard digitalis powder. Clinically it appeared that over a period of much more than one year the scillonin retained its potency. There was no notable deviation from the average dose necessary for therapeutic effect in any of the lots supplied to us. That the potency is well preserved over a long period will appear from an experience noted later in the paper. The average therapeutic dose was found by us to vary from 8 to 12 mg. (given over a period of four days) for the adult patient of average weight.

The cardiac rate as it is included in these reports was usually that recorded by the senior house physicians. During the period of more intensive treatment at least one daily record of the ventricular rate was made by this physician. These records were checked by one of us with sufficient frequency to satisfy us of their accuracy.

The charts of intake and output of fluid were under the direct supervision of the nurse in charge of the ward. The conditions in a large general hospital are not conducive to accuracy with respect to intake and output of fluid. The efficient service given by the head nurses, especially in the Cook County Hospital, made the charts of output presented here reliable. The standing orders included restriction of fluid to 1,500 cc. daily. In this article the term therapeutic effect

is used. By this term is meant that a dose was followed by definite clinical improvement, including recession of edema, disappearance of dyspnea while the patient was at rest, a fall in the ventricular rate and an increase in the urinary output. In practically all of our cases the initial large dose was followed by a maintenance dose, given for a variable period, of from 0.5 to 0.75 mg. daily.

There were 21 patients with rheumatic cardiac disease, to whom 23 courses of scillonin were given; 6 of these had formerly been patients in the hospital, 1 having a record of fifteen admissions to the Cook County Hospital within six years. Nine had a history of rheumatic cardiac disease over more than fourteen years. Every patient in the group had long been afflicted with cardiac disease. Of 14 patients who showed compensation, 6 were discharged from the hospital within two weeks of the beginning of medication and 11 within one month. There were 20 patients with arteriosclerotic cardiac disease, to whom

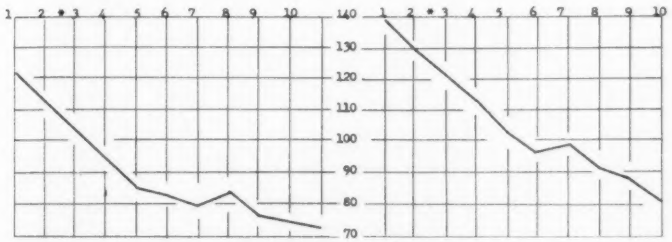

Chart 1.—The ventricular rate in 13 cases of auricular fibrillation with the administration of scillonin begun on the second or third day of hospitalization. The left-hand curve gives the rate of 9 patients who received 9 mg. or more in four days, or an average dose of 10.7 mg. Eight of this group were discharged from the hospital showing compensation within a period of from ten days to two months after scillonin therapy was started. One of the 2 patients who remained in the hospital for more than one month after scillonin therapy was started was allowed to suffer decompensation under our observation (the case is reported in chart 6). The other remained for some weeks to work in the ward. One patient, with severe decompensation, who died with symptoms of acute abdominal distress was shown at autopsy to have had a ruptured bladder. The right-hand curve gives the rate of 4 patients who received less than 9 mg. during the first four days, or an average dose of 7.25 mg. All the patients in this group were discharged from the hospital showing compensation within one month of the beginning of scillonin therapy. The asterisk indicates the approximate time of beginning the administration of scillonin.

26 courses of scillonin were given. Following 23 of the 26 courses the patients were discharged as improved. After 6 of the 26 courses the patients were discharged within two weeks. Six patients were in the hospital for more than a month after the medication was started. Three

patients died while under our care; 2 are known to have reentered the hospital and died shortly after their discharge from our service. To 16 patients with hypertensive cardiac disease 18 courses of the medication were given. Only 1 death occurred in this group. Six of the patients were discharged showing compensation within two weeks of the time the medication was started.

To 21 patients with cardiovascular syphilis 23 courses of the scillonin were given. Eighteen of these patients had aortic insufficiency; in 1 an aneurysm was diagnosed and found anatomically; in the case of 2 the diagnosis between hypertensive and syphilitic cardiac disease could not finally be made. Eleven of these patients died in our ward.

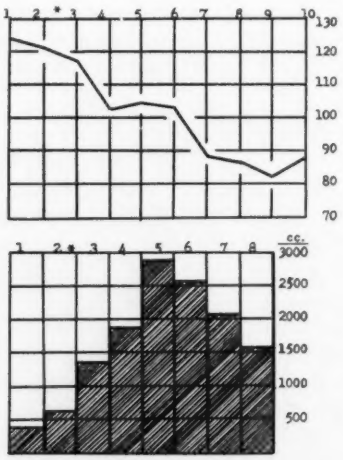

Chart 2.—The ventricular rate of 11 patients with auricular fibrillation and satisfactory records of urinary output. The average dose was 9 mg. in the first four days of therapy; in 5 instances less than 9 mg. was given in the first four days. All the patients in this group were discharged showing compensation, 7 within two weeks of the time scillonin therapy was started.

Another died in a different ward within three weeks of his discharge from our service; he had been discharged from our service showing compensation. The patient with the aneurysm also died within a short time in another ward. Thirteen of the 21 patients died while actually under our observation.

There were 7 patients with one of a miscellaneous group of cardiac diseases: 1 with subacute bacterial endocarditis, 1 with chronic emphysema, 1 with chronic glomerulotubular nephritis and acute endocarditis and 1 with gangrene complicating cardiac failure; only 1 of these 4 (the patient with emphysema) lived. There were 3 other cases in

which an etiologic diagnosis could not be made; these patients were all discharged showing compensation.

Satisfactory records of 14 courses of digitalis previously given to 11 patients in our series were found. For these 11 patients the average length of stay in the hospital under scillonin therapy was nineteen and three-tenths days; for the same patients through 14 courses of digitalis therapy the average duration of the stay in the hospital was eighteen and nine-tenths days. In seven of the fourteen courses of digitalis therapy the maximum therapeutic dosage was given.

One notable feature of the effect of scillonin is the long duration of its effect; marked slowing of the ventricular rate or bigeminal pulse

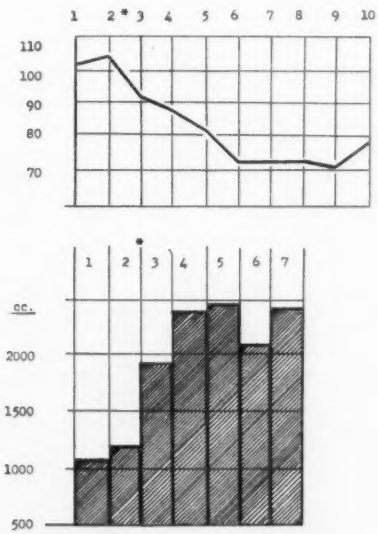

Chart 3.—Composite curves of the ventricular rate and urinary output of 17 patients for whom there was adequate control of the fluid output. Scillonin therapy was started on the third day of hospitalization. The average total dose for the first four days of administration was 8.8 mg. Two of the 17 died; both had cardiovascular syphilis. The other 15 were discharged showing compensation, 6 within two weeks and 7 in from eighteen to thirty days after scillonin therapy was started. One patient was not discharged until seven weeks after medication was started. Another showed compensation twelve days after scillonin therapy was started but remained in the hospital four months to work.

appeared in several instances several days after the medication had been stopped. In 1 case the ventricular rate, 64 when the medication was stopped, was 58 one week later. Another patient had a rate of 50 when medication was stopped; after five days the rate was 56. Bradycardia

developed in 1 patient, with a ventricular rate of 48 after 30 mg. of scillonin had been given in twenty-seven days; nine days thereafter the rate was 44, and on the twelfth day, 54. One patient with nausea and vomiting had a rate of 80 on the day the intoxication appeared. Although no more scillonin was given, the rate was 64 after four days and 60 after six days. Another patient with nausea had a rate of 60 when the scillonin therapy was stopped; eight days later the rate was 50. One patient with a ventricular rate of 48 showed occasional

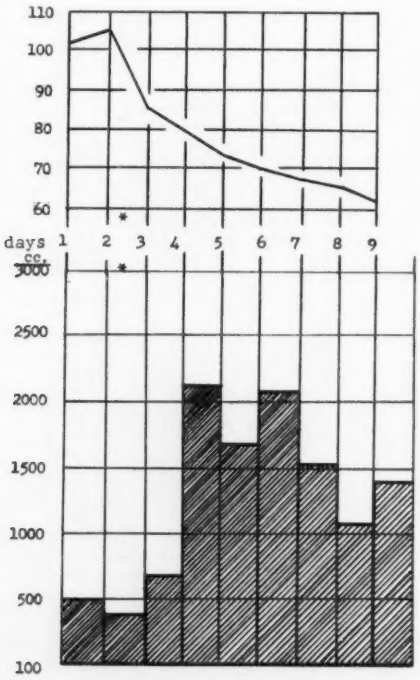

Chart 4.—Composites of the ventricular rate and urinary output of 9 patients to whom the estimated therapeutic dose was given in a short period. Two of these patients received 10 mg. within two days, 2 received 9 mg. within two days, and 1 received 10 mg. within one day, 1 received 12 mg. within three days and the other 3 received 11 mg. within three days. The chart of the urinary output is not satisfactory as it is made up of only six of the nine records. In 6 cases the therapeutic dose was followed by the daily administration of at least 1 mg. for from two to six days. In 2, cardiac irregularities developed: in 1 bigeminal pulse, and in the other, trigeminal pulse. In 1 patient the ventricular rate fell to 56 after 15 mg. of scillonin had been administered in 6 days. In 1 patient to whom 11 mg. was administered in three days auricular fibrillation developed with a ventricular rate of from 30 to 40 the day after the course of scillonin was completed. The group includes only 1 case of established auricular fibrillation.

periods of bigeminal pulse for two weeks after administration of the drug was discontinued. In another case the ventricular rate was 64 when medication was stopped; five days later the rate was 56. In another instance bigeminal pulse persisted for seven days after the scillonin therapy was discontinued.

In this series there were 29 instances in which the pulse (ventricular rate) fell to 60 or below in the course of the treatment, without cardiac irregularity. In one instance the bradycardia occurred in conjunction with an arrhythmia which was not identified. In 12 cases bigeminal pulse appeared. In 1 case trigeminal pulse was found. One patient had paroxysmal tachycardia (the nature of which was not determined) after 31.5 mg. of scillonin had been taken in twenty-three days. Auricular fibrillation developed in 3 patients in the course of the therapy with squill. The first instance of the onset of auricular fibrillation occurred in a man of 28 with rheumatic cardiac disease; the

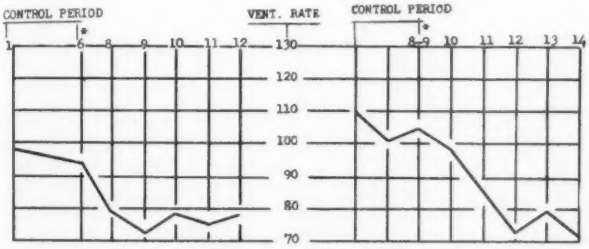

Chart 5.—Composites of the ventricular rate in 15 patients. The left-hand curve gives the rate of 9 patients. The control period was for five days, the maximum dose within four days was 14 mg., and the average dose within four days was 10.6 mg. In 2 of the earlier cases 8 mg. was given in the first four days, and 1 patient, a small Filipino of 19, received only 6 mg. in four days. The right-hand curve gives the rate of 6 patients. The control period was for eight or nine days, the maximum dose within four days was 14 mg., and the average dose within four days was 10.3 mg. In 1 case only 8 mg. was given within the first four days of treatment. Twelve of the 15 patients were discharged showing compensation after periods of from one to four weeks following the beginning of scillonin medication. One patient showed compensation promptly but was in the hospital for ten weeks because of complicating diabetes. One patient with low grade acute endocarditis and congestive failure was discharged showing compensation after twelve weeks. One patient with a cerebral hemorrhage, to whom scillonin was given merely to control the ventricular rate, died.

administration of scillonin was continued in daily doses of 1 mg. The fibrillation persisted through four days. The second case was that of a woman of 46 with cardiovascular syphilis and hypertension, in whom fibrillation developed after 36 mg. had been taken in twenty-six days.

The administration of scillonin was discontinued, and within five days the normal mechanism was reestablished. In the third case 11 mg. of scillonin was given within three days, following which the fibrillation appeared. The normal mechanism reappeared after five days.

Nausea was present in 12 patients. In 2 gastric distress and nausea were present at the time of admission and disappeared as the scillonin produced its favorable effect on the circulation. There were therefore 10 cases in which nausea was attributable to the scillonin. In 1 instance, coincidental with the appearance of bigeminal pulse, the patient stated that he could "easily be nauseated." In 3 instances cardiac irregularity or pronounced bradycardia preceded the nausea; in 1 instance bradycardia and in another bigeminal pulse were discovered when the nausea

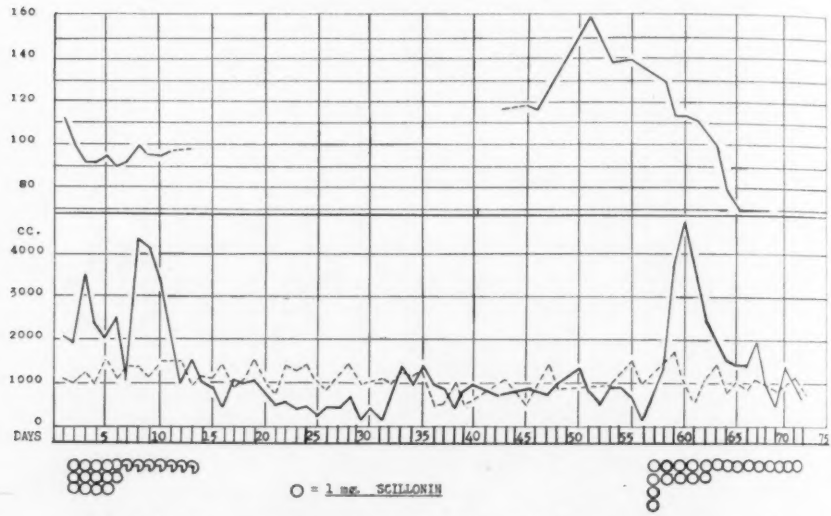

Chart 6.—The upper curve represents the ventricular rate, the lower solid curve the urinary output and the broken curve the fluid intake of 1 patient (case 44). Scillonin therapy was started on the second day of hospitalization and was discontinued after thirteen days. No scillonin or other drug of the digitalis group was given thereafter until the fifty-seventh day. Meanwhile, after thirty-two days without medication other than an occasional dose of magnesium sulphate the patient showed signs of decompensation. He was allowed to be up and about the ward for six days. By this time he showed marked decompensation, with the ventricular rate 160. He was put to bed for six days with no medication except an occasional dose of morphine. Scillonin therapy was recommenced on the fifty-seventh day.

was first reported, and twice the cardiac irregularity followed closely on the complaint of nausea. Twice nausea occurred alone. Nausea in the course of scillonin medication is not the relatively mild early sign

of intoxication with which one is familiar in the course of digitalis therapy. The nausea of scillonin intoxication signifies a marked degree of intoxication and calls for the immediate discontinuance of the drug.

In 9 of the 29 cases in which marked bradycardia occurred the slow rate came on after rather small doses of scillonin were given; in each case less than 10 mg. was administered in periods ranging from two to seven days, and the average dose was 8.25 mg. In 5 of these 9 cases digitalis had probably been given within a short time prior to admission to the hospital; in 1 a course of scillonin had been discontinued three weeks earlier. Of the 13 patients with bigeminal pulse, in only 3 did the rhythm develop when less than 10 mg. of scillonin had been taken, and

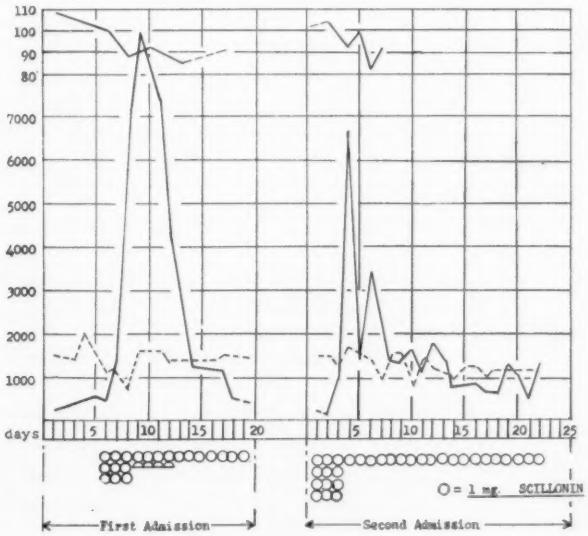

Chart 7.—The upper curve represents the ventricular rate, the lower solid curve the urinary output and the broken curve the fluid intake of 1 patient (case 48). The record of the first admission shows the result of scillonin medication started on the sixth day of hospitalization. The record of the second admission, six weeks after the first, shows the result of scillonin medication started on the first day.

2 of these 3 had taken digitalis within a period of a week or more. Of the patients with bradycardia, 8 had taken squill for ten days or more. The duration of medication varied from ten to twenty-eight days, and the total dosage, from 12 to 33 mg. An average for each patient of 20.7 mg. was taken during fifteen and seven-tenths days. Ten patients in whom bigeminal pulse developed received from 13 to 30 mg. in periods varying from nine to twenty-three days, an average of

18.5 mg. within nine and eight-tenths days. Nine patients who became nauseated received from 7 to 24 mg. over periods varying from three to twenty-one days, an average of 17 mg. in ten and six-tenths days. It appears that the total dose likely to produce nausea is about the same as that which produces cardiac irregularity, although in these small groups nausea appeared following a smaller average daily dose than was necessary to produce cardiac irregularity.

There were 2 deaths attributable to the scillonin. In spite of emphasis on the importance of discontinuing the administration of scillonin if any signs of digitalis intoxication appeared, a patient was allowed to receive 5 mg. through two and one-half days after nausea developed. He died two days after the drug was withdrawn. He did not have a cardiac rate below 68, nor did he show cardiac irregularity. He presented a late stage of cardiovascular syphilis with marked anemia. In another ward than our own a patient with long-standing rheumatic disease, advanced decompensation and digitalis intoxication was treated for five days with rest, promoted by an occasional dose of morphine. Scillonin therapy was then started, 3 mg. administered daily for two days, followed by 2 mg. every day for three days. On the third day of this routine the pulse was "irregular"; on the fourth day nausea was present, and on the fifth day the patient died. It cannot be too clearly stated that scillonin manifests all the therapeutic and toxic effects of digitalis. It produces the usual effects of digitalis, because of which it is valuable in the treatment of cardiac decompensation. It is not to be used as a substitute for digitalis in the presence of digitalis intoxication.

SUMMARY

1. Scillonin, a derivative of squill, will produce the usual effects of digitalis in the treatment of cardiac decompensation. Essentially the same therapeutic and toxic results are obtained as occur with the use of digitalis.

2. In our experience cardiac irregularities are likely to be the first signs of dangerous intoxication. Nausea does occur and may precede the appearance of cardiac irregularities. The nausea of scillonin intoxication is significant in that it appears to signify a more advanced grade of intoxication than that associated with the nausea of digitalis. Nausea and cardiac irregularities occurring in the course of treatment with scillonin are symptoms which call for the immediate discontinuance of administration of the drug.

3. Slowing of the cardiac rate to 60 or below is frequent with the successful use of scillonin. The onset of a rate as low as 60 is significant of the full therapeutic dose and calls for discontinuance of scillonin medication temporarily.

4. A dose of from 8 to 12 mg. of scillonin of standard potency as now provided, depending on the weight of the patient, may be given within four days to patients who are known to have taken no drug of the digitalis group within two weeks. If a prior course of scillonin or of some other drug of the digitalis group has been used with full therapeutic effect, the maximum dosage of scillonin should not be repeated within a month. Under these circumstances small doses may be given daily until the effect appears. The maintenance dose of scillonin is approximately 0.5 mg. per day, but it must be adapted to the needs and response of the individual patient. In a few cases in private practice the patient has been kept on a small daily ration for three years or more. For small patients the daily maintenance dose is as low as 0.33 mg.

5. Scillonin therapy is of advantage to certain persons who take digitalis with difficulty because of gastric distress early in the course of medication. Scillonin may be recommended for these patients. It is not a substitute for digitalis in the presence of frank digitalis intoxication. When digitalis has been given recently only small doses of scillonin are permissible. The desired effect may be achieved by daily doses somewhat larger than the maintenance dose.

6. Scillonin retains its potency over a long period. A supply in our possession for about seventeen months proved as effective at the end of that time as the lots recently assayed.

EFFECT OF DIGITALIS ON THE CARDIAC OUTPUT OF PERSONS WITH CONGESTIVE HEART FAILURE

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The observations to be presented in this report constitute a part of a general study of the functional alterations concerned in the production of the clinical picture of congestive heart failure. One method of obtaining information concerning such alterations is to inquire into the mechanism whereby therapeutic measures produce clinical improvement. It is now generally recognized not only that digitalis is the sovereign remedy for heart failure in patients with auricular fibrillation but that this drug is often beneficial to persons with regular rhythm. In the former group of patients clinical improvement may be ascribed to the dramatic slowing of the heart, but in the latter group changes in the cardiac rate are usually slight, and an adequate explanation for the benefits from digitalis has yet to be offered. According to some investigators, the effects are dependent on an increase in the output of the heart per minute; other authors have expressed the opinion that the drug has the reverse effect.

In the isolated heart of the frog digitalis causes an increase in the strength of the contraction, so that the heart empties itself more completely. Similar effects may be noted in a perfused mammalian heart. The output per beat is therefore usually increased, and the output per minute may or may not be increased, according to whether the greater contraction does or does not predominate over the diminished rate of the heart.[1]

Various results have been arrived at by workers who have utilized the heart-lung preparation to study the effects of digitalis. Bijelsma and

From the Department of Medicine, Vanderbilt University School of Medicine.

1. Cushny, A. R.: Textbook of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1928.

Roessingh [2] observed that strophanthin diminished the size of the heart but did not change its output, and similar observations were reported by Bodo [3] with digitalis. Plant [4] studied hearts which had been poisoned by phosphorus and noted that strophanthin caused a temporary increase in the amplitude of contraction. Cohn and Steele [5] administered digitalis to hearts which were failing, as shown by a rise in the auricular pressure and a decrease in the output. The drug caused a temporary reversal of these effects, the output increasing and the auricular pressure diminishing.

On the other hand, digitalis has been shown to diminish the output of the heart of normal dogs (Harrison and Leonard [6]; Cohn and Stewart [7]; Dock and Tainter [8]) and of normal human beings (Burwell, Neighbors and Regen [9]; Stewart and Cohn [10]).

Concerning the effect of the drug on the cardiac output of patients with cardiac disease, there is considerable doubt. Increase in the output

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2. Bijelsma, U. G., and Roessingh, M. J.: Die Dynamik des Säugetierherzens unter dem Einfluss von Stoffen der Digitalisgruppe, Arch. f. exper. Path. u. Pharmacol. **94**:235, 1922.

3. Bodo, R.: The Effect of the "Heart-Tonics" and Other Drugs upon the Heart-Tone and Coronary Circulation, J. Physiol. **64**:365, 1928.

4. Plant, O. H.: A Note on the Efficiency of the Knowlton-Starling Isolated Heart-Lung Preparation for Testing the Cardiac Action of Drugs, J. Pharmacol. & Exper. Therap. **5**:603, 1913-1914.

5. Cohn, A. E., and Steele, J. M.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: I. The Effect on the Output of the Dog's Heart in Heart-Lung Preparations, J. Clin. Investigation **11**:871, 1932.

6. Harrison, T. R., and Leonard, B. W.: The Effect of Digitalis on the Cardiac Output of Dogs and Its Bearing on the Action of the Drug in Heart Disease, J. Clin. Investigation **3**:1, 1926.

7. Cohn, A. E., and Stewart, H. J.: The Relation Between the Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Normal Dogs, J. Clin. Investigation **6**:53, 1928; The Relation Between the Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Dogs in Which the Heart Is Enlarged, ibid. **6**:79, 1928.

8. Dock, W., and Tainter, J. L.: The Circulatory Changes After Full Therapeutic Doses of Digitalis, with a Critical Discussion of Views on the Cardiac Output, J. Clin. Investigation **8**:467, 1929.

9. Burwell, C. S.; Neighbors, D. W., and Regen, E. M.: The Effect of Digitalis on the Output of the Heart in Normal Man, J. Clin. Investigation **5**:125, 1927.

10. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: Effect on the Output of Hearts of Dogs Subject to Artificial Auricular Fibrillation, J. Clin. Investigation **11**:897, 1932; Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart; the Effect on the Output in Normal Human Hearts; the Effect on the Output of Hearts on Heart Failure with Congestion, in Human Beings, ibid. **11**:917, 1932.

was reported by Ringer and Altschule [11] and likewise by Lauter and Baumann,[12] who used the method employing ethyl iodide. Eppinger, von Papp and Schwarz [13] and Schwarz,[14] employing a modification of an indirect Fick method employing oxygen, reported that digitalis caused a decrease in the cardiac output. Ewig and Hinsberg,[15] with the method employing carbon dioxide, observed no change in the cardiac output following the administration of digitalis; and Kininmonth,[16] with the ethyl iodide procedure, found that clinical improvement following the administration of digitalis might be associated with an increase, with a decrease or with no change in the minute output of the heart.

Recent studies of Grollman [17] have cast doubt on the validity of these various methods, even in normal subjects, and their applicability to persons with cardiac disease is therefore dubious. On the other hand, Grollman has presented convincing evidence of the reliability in normal subjects of his method employing acetylene. In view of this evidence, the observations of Stewart and Cohn,[10] who studied the effect of digitalis in persons with cardiac disease by means of the acetylene method are entitled to special consideration. These authors reported a consistent increase in the output of the heart per minute following the administration of digitalis to six of seven subjects suffering from a failing heart. After their paper had been published, a critical study of the reliability of methods for determining the cardiac output of patients with cardiac disease was made by Grollman, Friedman, Clark and Harrison.[18] They found that it is impossible to obtain accurate results in certain patients with cardiac failure but that in other patients reliable data can be procured provided a minor modification is introduced into

11. Ringer, M., and Altschule, M.: Studies on the Circulation: II. Cardiac Output in Diseases of the Heart and Under the Influence of Digitalis Therapy, Am. Heart J. **5**:305, 1929.

12. Lauter, S., and Baumann, H.: Zur Theorie der Herzinsuffizienz und der Digitaliswirkung, Klin. Wchnschr. **8**:263, 1929.

13. Eppinger, H.; von Papp, L., and Schwarz, H.: Ueber das Asthma cardiale, Berlin, Julius Springer, 1924.

14. Schwarz, H.: Zur Theorie der Herzinsuffizienz und der Digitaliswirkung: Kritische Bemerkungen zur Arbeit von Lauter und Baumann, Klin. Wchnschr. **8**:599, 1929.

15. Ewig, W., and Hinsberg, K.: Neue Methode zur Bestimmung des Herzminutenvolumens, Ztschr. f. klin. Med. **115**:677, 1931.

16. Kininmonth, J. G.: The Circulation Rate in Some Pathological States, with Observations on the Effect of Digitalis, Quart. J. Med. **21**:279, 1928.

17. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

18. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12**:751, 1933.

the technic and certain criteria are fulfilled. In the absence of such controls results in error by as much as 50 per cent were sometimes encountered, and seriously fallacious data were frequently obtained. The observations of Grollman and his colleagues cast doubt on the validity of the conclusions drawn by Stewart and Cohn, and therefore we have felt that the problem should be restudied, with the newer technic, which not only is free from certain theoretical errors but has been checked against another more laborious method based on an entirely different principle.[19]

METHOD

The subjects studied were adults with various degrees of congestive heart failure dependent on the usual etiologic factors. Since it was often impossible to obtain accurate results in patients with marked decompensation, the subjects chosen usually presented mild or moderate congestive phenomena. They were trained to the rebreathing procedure for one or more days prior to the beginning of the observations. Several of the subjects had been examined previously and were accustomed to respiratory gymnastics.

The plan of procedure was as follows: The patient, in the basal condition, was brought to the laboratory in a wheel-chair. The consumption of oxygen was determined in duplicate by analysis of the expired air with the Haldane apparatus. The technic used for measuring the arteriovenous oxygen difference was that described in previous papers.[20] Two rebreathings were usually done, the samples of gas being obtained at approximately twenty-two, twenty-six and thirty seconds in the first and two seconds later in the second. The time of sampling was varied somewhat according to previous knowledge of the subject's ability to secure a mixture in the lung-bag system and of the time at which recirculation occurred. When the subject breathed poorly or failed to empty the bag completely, the observation was discarded.

During the control period, the patients were kept at rest in bed and ordinarily received no therapy other than sedatives and limitation of food and fluids. In a few instances diuretics were given prior to the administration of digitalis. Following one or more successful determinations of the cardiac output, digitalis was administered, the usual dose being 1.5 Gm. of a standardized powdered leaf on the first day, from 0.3 to 0.6 Gm. of the standardized powdered leaf on the second day and a daily maintenance dose of 0.2 Gm. thereafter.

The patients studied were divided into three groups on the basis of their clinical response to digitalis. Definite improvement was considered to have occurred when one or more of the following phenomena appeared during the first three days of administration of digitalis: (1) diuresis, as shown by rapid decrease in the body weight; (2) a rise in the vital capacity of 15 per cent or more, and (3) cessation of paroxysmal dyspnea, which had been persistent prior to the administration of digitalis. A patient was classified as exhibiting questionable improvement when, in addition to his subjective claim that dyspnea was improved,

19. Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXII. A Method for Obtaining "Mixed" Venous Blood by Arterial Puncture, J. Clin. Investigation **13**:533, 1934.

20. Grollman, Friedman, Clark and Harrison.[18] Friedman, Clark and Harrison.[19]

TABLE 1.—*Observations on Patients Showing Definite Improvement After the Administration of Digitalis*

Patient	Diagnosis	Date 1933	Dyspnea*	Edema	Weight, Pounds	Vital Capacity, Liters	Heart Rate	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen, Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Cardiac Output, Liters per 100 Cc. of Oxygen Absorbed	Cardiac Output per Minute, Liters per Square Meter	Duration of Administration of Digitalis, Days	Total Amount of Digitalis Given, Gm.	Comment
J. E.	Hypertension	2/24	++++	++	138	2.05	..	241	84.6	2.85	1.18	1.83	..	0	Paroxysmal
		3/ 3	+++	+	123	2.30	88	184	93.7	2.07	1.07	1.33	..	0	dyspnea
		3/ 6	+	0	116	2.50	76	192	80.0	2.45	1.25	1.57	3	2.1	ceased
		3/ 7	+	0	115	2.00	73	214	91.6	2.34	1.09	1.50	4	2.3	
		3/ 8	+	0	116	2.00	74	221	85.2	2.59	1.17	1.66	5	2.5	
		3/ 9	+	0	116	2.85	70	169	70.0	2.42	1.43	1.55	6	2.7	
		3/10	+	0	115	2.70	66	179	78.8	2.28	1.27	1.46	7	2.9	
		3/11	+	0	115	2.70	66	199	85.8	2.32	1.17	1.49	8	3.1	
H. M.	Hypertension	5/18	+++	0	217	2.75	58	225	66.3	3.39	1.51	1.67	..	0	Paroxysmal
		5/19	+++	0	216	2.75	61	220	66.4	3.31	1.51	1.63	..	0	dyspnea
		5/20	++	0	214	2.85	61	208	45.4	4.58	2.20	2.26	1	1.5	ceased
		5/22	+	0	214	3.00	62	220	75.3	2.92	1.33	1.44	3	2.5	
		5/23	+	0	214	3.10	61	206	68.9	2.99	1.45	1.47	4	2.8	
G. B. S.	Hypertension, auricular fibrillation	8/ 9	++++	++	196	1.50	89	319	85.7	3.82	1.17	1.96	..	0	Paroxysmal
		8/11	+++	++	194	1.70	92	307	90.2	3.40	1.11	1.74	..	0	dyspnea
		8/13	++	++	190	1.80	84	304	76.4	3.98	1.31	2.04	1	1.5	ceased
		8/14	+	++	192	1.93	79	295	98.4	3.30	1.02	1.69	2	2.1	
		8/16	+	++	193	1.95	82	305	74.0	4.12	1.35	2.11	4	2.7	
M. O.	Hypertension, auricular fibrillation	8/ 7	+++	+	290	3.10	75	382	89.5	4.28	1.12	1.78	..	0	Paroxysmal
		8/ 8	+++	+	288	3.00	69	362	82.6	4.38	1.21	1.82	..	0	dyspnea
		8/ 9	++	+	287	3.20	75	378	90.2	4.18	1.11	1.72	1	1.5	ceased
		8/10	++	+	286	3.50	70	407	104.5	3.89	0.96	1.62	2	2.1	
		8/11	+	0	284	3.60	70	378	103.1	3.68	0.97	1.53	3	2.5	
		8/12	+	0	285	3.40	72	403	106.0	3.80	0.94	1.58	4	2.9	
I. M.	Mitral stenosis, auricular fibrillation	12/12	++++	+	126	2.20	128	245	101.9	2.40†	0.98	1.56	..	0	
		12/14	+	0	122	2.60	84	216	96.6	2.37	1.03	1.54	1	1.7	
		12/16	+	0	121	2.80	74	206	85.7	2.40	1.17	1.56	3	2.1	
A. E.	Syphilitic myocarditis	2/20	++++	+++	165	1.85	90	254	88.1	2.89	1.13	1.62	..	0	Paroxysmal
		2/21	++++	+++	165	1.95	91	247	85.0	2.91	1.18	1.63	..	0	dyspnea
		2/22	+++	+++	165	1.90	85	247	68.9	3.59	1.45	2.02	1	1.5	ceased
		2/23	+++	+++	161	2.05	74	248	71.1	3.48	1.41	1.96	2	2.3	
		2/27	++	+	145	2.65	70	236	79.6	2.96	1.26	1.66	6	3.12	
		2/28	+	+	143	2.80	68	200	67.2	2.98	1.49	1.67	7	3.3	
		3/ 2	+	0	138	2.90	68	232	86.6	2.92	1.15	1.64	9	3.5	
		3/ 6	+	0	138	3.00	66	252	71.5	3.52	1.40	1.98	13	4.3	
		3/ 7	+	0	138	3.00	66	278	78.0	3.52	1.28	1.98	14	4.5	
		3/ 8	+	0	137	3.00	72	247	77.8	3.18	1.28	1.79	15	4.7	
C. M.	Syphilitic aortic insufficiency	7/26	+++	++	144	2.10	84	205	94.9	2.16	1.05	1.34	..	0	Paroxysmal
		7/27	+++	++	144	1.75	80	196	98.8	1.98	1.01	1.23	..	0	dyspnea
		7/28	++	++	143	2.35	66	211	90.8	2.32	1.10	1.44	1	1.6	ceased
		7/29	++	++	145	2.10	62	222	77.0	2.88	1.30	1.79	2	1.9	
		8/ 1	+	0	131	2.40	62	214	97.5	2.19	1.03	1.36	5	2.7	
A. M.	Syphilitic aortic insufficiency	8/24	+++	++	163	2.50	76	272	112.6	2.42	0.89	1.38	..	0	Received
		8/25	+++	++	161	2.60	76	290	113.8	2.55	0.88	1.46	..	0	salyrgan
		8/26	++	+	151	2.90	78	278	117.9	2.36	0.85	1.35	..	0	
		8/27	+	+	147	3.15	71	254	105.4	2.41	0.95	1.38	1	0.6	
		8/28	+	0	143	3.15	73	251	97.9	2.56	1.02	1.46	2	1.2	
		8/29	+	0	143	3.40	66	230	119.2	1.93	0.84	1.10	3	1.8	
		8/30	+	0	144	3.20	69	236	118.8	2.02	0.85	1.15	4	2.4	
		8/31	+	0	144	3.20	62	224	100.6	2.23	0.99	1.27	5	2.6	
		9/ 1	+	0	143	3.25	64	224	105.4	2.12	0.95	1.21	6	2.8	

* In this and the following tables the symbols +, ++, +++ and ++++ refer, respectively, to dyspnea on moderate exertion, dyspnea on slight exertion, dyspnea on exertion plus slight dyspnea while at rest and dyspnea on exertion plus moderate dyspnea while at rest.

† The cardiac output of this patient was determined by the venous plateau method.

there occurred either a rise in vital capacity of less than 15 per cent or a cessation of previously intermittent paroxysmal dyspnea. Subjects who showed neither well defined subjective nor well defined objective changes after the administration of digitalis were classified as unimproved.

In analysis of the data, changes of less than 10 per cent in the cardiac output and arteriovenous oxygen difference were not considered significant, because the analytic procedures involve a possible error of this general magnitude.

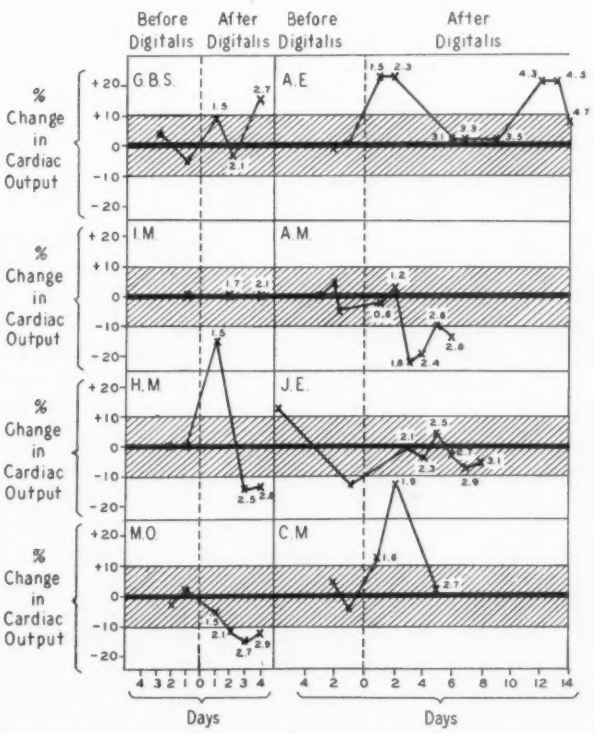

Chart 1.—The data are plotted for the subjects who exhibited definite improvement following the administration of digitalis. The central bar represents the average value for the cardiac output before the administration of digitalis. Changes within 10 per cent of this (represented by the shaded areas) are not considered significant; the numbers refer to the total amount (in grams) of digitalis received at the time of the observation.

RESULTS

According to Grollman,[17] who investigated a large group of healthy subjects, the normal cardiac output is 2.2 ± 0.3 liters per square meter of body surface. Prior to the administration of digitalis the range of values in our patients was between 1.34 and 2.09 liters per square meter,

the values being below Grollman's normal range in thirty-five of forty-two determinations on twenty-two subjects. Per hundred cubic centimeters of oxygen absorbed the cardiac output of the patients before receiving digitalis was from 0.85 to 1.52 liters, being less than 1.4 liters, the lower normal limit in thirty-six of forty-two observations. These data are in agreement with our previous report [21] that the cardiac output is usually subnormal but may be within normal limits in persons with congestive heart failure.

The data on the eight patients who exhibited definite improvement following the administration of digitalis are shown in table 1 and chart 1. Following the administration of the drug, dyspnea became less marked or disappeared in all the patients, and paroxysmal dyspnea ceased in the six patients who showed it prior to administration of the drug. Seven of the subjects had edema of some degree, and in six it disappeared. The vital capacity of each subject increased. One of the patients (I. M.) had auricular fibrillation with a rapid ventricular rate, which diminished to normal following the administration of the drug. Two patients with fibrillation with a slower ventricular rate had less striking changes in the heart rate. The heart rate became slower in four of the five patients with normal rhythm. The consumption of oxygen per minute was definitely less after the administration of digitalis in two subjects (I. M., A. M.) and was unchanged or showed variations in the others.

An increase in the cardiac output was evident at four of eight examinations in one of the eight subjects (A. E.). Two patients (A. M.; M. O.) showed a slight decrease in the output of the heart per minute at two or three examinations. In one patient (I. M.), who showed marked improvement following digitalis therapy, no change in the cardiac output was revealed at either of two examinations. The remaining four subjects exhibited inconstant fluctuations.

The arteriovenous oxygen difference, which is an inverse measure of the cardiac output in proportion to metabolism, likewise failed to undergo constant change. A significant diminution in the arteriovenous difference occurred in two subjects (I. M.; A. E.); a significant increase occurred in one patient (M. O.), and fluctuations in either direction were noted in the other subjects.

Eleven patients were classified as exhibiting questionable (i.e., chiefly subjective) improvement following digitalis therapy. In these persons fluctuations in the cardiac output occurred (table 2, chart 2).

21. Harrison, T. R.; Friedman, Ben; Clark, Gurney, and Resnik, Harry: The Cardiac Output in Relation to Cardiac Failure, Arch. Int. Med. **54**:239 (Aug.) 1934.

TABLE 2.—OBSERVATIONS ON PATIENTS SHOWING CUMULATIVE IMPROVEMENT AFTER THE ADMINISTRATION OF DIGITALIS

Patient	Diagnosis	Date 1933	Dyspnea	Edema	Weight, Pounds	Vital Capacity, Liters	Heart Rate	Oxygen Consumption per Minute, Cc.	Arterio-venous Oxygen, Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Cardiac Output, Liters per 100 Cc. of Oxygen Absorbed	Cardiac Output per Minute, Liters per Square Meter	Duration of Administration of Digitalis, Days	Total Amount of Digitalis Given, Gm.	Comment
P. F.	Hypertension	3/30	++	0	176	2.30	84	249	75.6	3.30	1.32	1.78	..	0	Paroxysmal
		3/31	++	0	175	2.40	77	245	79.0	3.11	1.27	1.68	..	0	dyspnea
		4/ 4	+	0	174	2.35	68	237	60.8	3.90	1.67	2.11	4	2.7	ceased
		4/ 5	+	0	173	2.50	76	241	80.6	2.98	1.24	1.61	5	3.0	
		4/ 7	+	0	173	2.40	62	236	59.6	3.95	1.68	2.14	7	3.2	
		4/ 8	+	0	174	2.50	64	222	65.5	3.39	1.53	1.83	8	3.4	
L. M.	Hypertension	3/21	+++	±	163	2.20	96	247	99.9	2.47	1.01	1.36	..	0	Paroxysmal
		3/23	++	±	163	2.20	94	254	81.1	3.12	1.23	1.71	1	1.5	dyspnea
		3/24	++	0	160	2.45	90	273	89.7	3.07	1.12	1.69	2	1.9	ceased
		3/25	++	0	160	2.35	85	264	94.2	2.81	1.06	1.54	3	2.2	
		3/27	++	0	159	2.50	86	262	94.8	2.76	1.06	1.52	5	2.6	
J. M.	Hypertension	11/ 4	++	0	148	3.00	80	219	82.0	2.67*	1.22	1.48	..	0	Paroxysmal
		11/ 5	++	0	144	2.90	77	235	83.8	2.80	1.19	1.56	..	0	dyspnea
		11/ 7	+	0	146	2.90	58	233	72.7	3.20	1.38	1.78	2	2.0	ceased
		11/ 9	+	0	147	3.15	64	231	70.3	3.28	1.42	1.82	4	2.4	
M. B.	Hypertension	6/12	+	0	...	2.60	60	240	75.8	3.17	1.32	1.71	..	0	
		6/14	++	0	...	2.90	58	242	76.7	3.16	1.30	1.71	1	1.0	
		6/16	+	0	...	2.60	56	247	74.2	3.33	1.35	1.80	3	1.7	
		6/17	+	0	...	2.65	60	263	87.2	3.01	1.15	1.63	4	1.9	
T. K.	Hypertension, arteriosclerosis	5/29	++	+	185	2.85	74	308	100.7	3.04	0.99	1.58	0	0	
		6/ 3	+	+	183	2.80	59	292	102.6	2.88	0.97	1.50	5	2.2	
M. P.	Mitral stenosis, auricular fibrillation	4/26	+++	+	125	1.60	76	173	74.7	2.32	1.34	1.60	..	0	
		4/29	+++	+	125	1.50	70	208	72.0	2.85	1.39	1.97	..	0	
		5/ 2	++	+	124	1.65	56	171	71.7	2.39	1.39	1.65	2	2.1	
		5/ 3	++	+	124	1.70	52	193	75.8	2.55	1.32	1.76	3	2.4	
L. W.	Mitral stenosis	8/ 2	++	0	119	3.05	68	239	70.5	3.38	1.42	2.09	..	0	
		8/ 7	++	0	121	3.00	84	224	66.0	3.39	1.52	2.09	..	0	
		8/ 9	++	0	121	3.00	66	210	66.3	3.17	1.50	1.96	2	2.0	
		8/11	++	0	120	3.30	69	223	78.7	2.82	1.27	1.74	4	2.6	
		8/12	++	0	119	3.10	80	212	83.3	2.55	1.20	1.58	5	2.9	
M. L.	Mitral stenosis, auricular fibrillation	4/27	++	0	126	2.00	88	187	91.1	2.05	1.10	1.36	..	0	
		4/28	++	0	127	2.00	80	182	83.2	2.19	1.20	1.45	..	0	
		4/30	+	0	127	2.30	92	173	96.5	1.79	1.04	1.19	1	1.5	
		5/ 3	+	0	127	2.20	72	187	96.8	1.93	1.03	1.28	2	2.1	
		5/ 2	0	0	126	2.20	72	205	103.6	1.98	0.97	1.31	3	2.4	
		5/ 4	0	0	127	2.10	80	179	89.4	2.00	1.12	1.32	5	3.0	
A. T.	Mitral stenosis	7/22	++	++	96	1.70	82	186	87.5	2.13	1.14	1.70	..	0	
		7/24	++	++	97	1.60	80	235	108.9	2.16	0.92	1.73	..	0	
		7/25	++	++	97	1.80	98	200	106.7	1.88	0.94	1.51	..	0	
		7/26	++	++	95	1.60	82	156	89.1	1.75	1.12	1.40	1	1.2	
		7/28	++	++	95	1.65	70	171	75.8	2.25	1.32	1.80	3	1.6	
		7/29	++	++	95	1.75	72	185	100.2	1.85	1.00	1.48	4	1.8	
Y. D.	Syphilitic aortic insufficiency	6/ 6	++	0	136	2.55	84	263	105.5	2.38	0.95	1.43	..	0	Paroxysmal
		6/ 7	++	0	136	2.70	75	252	102.2	2.47	0.98	1.48	..	0	dyspnea
		6/ 8	++	0	134	2.60	69	239	89.6	2.67	1.12	1.60	1	1.5	ceased
		6/ 9	+	0	136	2.50	62	249	98.7	2.52	1.01	1.51	2	2.4	
		6/10	+	0	137	2.55	63	227	94.1	2.41	1.06	1.44	3	2.7	
G. M.	Syphilitic myocarditis	9/ 8	++	++	145	1.90	74	251	78.0	3.21	1.28	1.96	..	0	
		8/11	++	+	135	2.00	80	225	67.0	3.39	1.50	2.07	..	0	
		8/13	++	+	137	2.00	78	241	76.0	3.19	1.32	1.95	..	0	
		9/15	+	0	131	2.20	82	238	80.0	2.68	1.12	1.64	2	1.2	
		9/16	+	0	132	2.00	79	223	79.0	2.81	1.27	1.71	3	1.8	
		9/18	+	0	132	2.10	72	225	91.0	2.48	1.10	1.51	4	2.0	

* The cardiac output of this patient was determined by the venous plateau method.

Following the administration of the drug, the cardiac output tended to be higher in three subjects, lower in three subjects and unchanged in the remaining five. The arteriovenous oxygen difference was, in general, somewhat less in five subjects, slightly greater in two and unchanged in four.

Three subjects failed to show evidence of improvement following the administration of digitalis (table 3). One had a decrease in the cardiac output; another, an increase, and the third, no change.

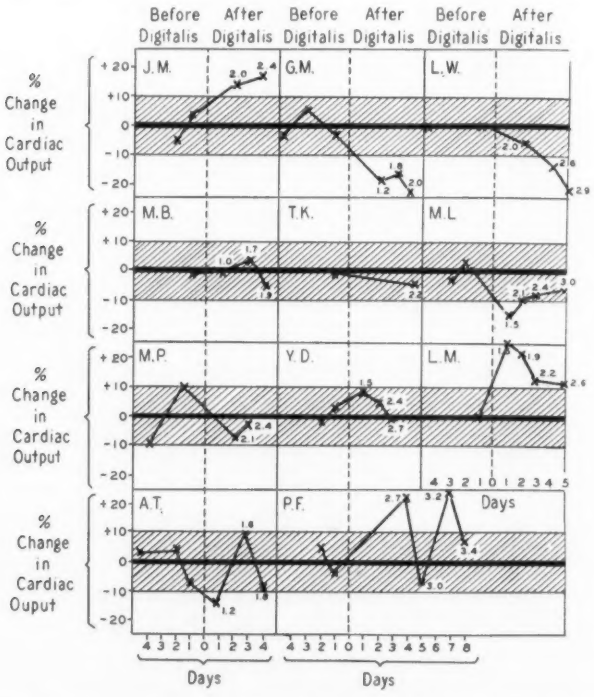

Chart 2.—The data are plotted for the subjects who exhibited questionable improvement following the administration of digitalis. The central bar represents the average value for the cardiac output before the administration of digitalis. Changes within 10 per cent of this are not considered significant. The numbers refer to the total amount (in grams) of digitalis received at the time of observation.

In the entire group of twenty-two patients five persons had an average increase of more than 10 per cent in the cardiac output per minute following treatment with digitalis. Improvement was definite in two, questionable in two and absent in one. Four patients had an

TABLE 3.—*Observations on Patients Showing No Improvement After the Administration of Digitalis*

Patient	Diagnosis	Date 1933	Dyspnea	Edema	Weight, Pounds	Vital Capacity, Liters	Heart Rate	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Cardiac Output, Liters per 100 Cc. of Oxygen Absorbed	Cardiac Output per Minute, Liters per Square Meter	Duration of Administration of Digitalis, Days	Total Amount of Digitalis Given, Gm.
R. O.	Hypertension	2/18	++	+	136	2.75	82	187	68.4	2.74	1.46	1.78	..	0
		2/22	++	+	136	2.70	88	178	73.7	2.41	1.36	1.57	..	0
		2/25	++	+	136	2.70	80	191	71.8	2.66	1.39	1.73	3	2.0
		2/26	++	+	136	2.70	91	165	83.4	1.98	1.20	1.29	4	2.3
S. F.	Rheumatic aortic insufficiency	4/17	++	0	...	3.80	66	226	78.3	2.89	1.28	1.73	..	0
		4/18	++	0	...	3.65	70	238	77.8	3.06	1.29	1.83	..	0
		4/19	++	0	...	4.00	70	243	64.4	3.77	1.55	2.26	1	1.5
		4/20	++	0	...	4.13	68	216	68.1	3.18	1.47	1.90	2	2.1
		4/21	++	0	...	4.25	67	207	66.7	3.10	1.50	1.86	3	2.4
		4/22	++	0	...	3.85	60	205	65.8	3.12	1.52	1.87	4	2.7
F. B.	Syphilitic aortic insufficiency	7/15	+++	++	155	1.90	..	247	102.4	2.41	0.98	1.44	..	0
		7/18	+++	+++	166	1.80	..	238	88.5	2.68	1.13	1.61	1	1.5
		7/19	+++	+++	161	1.70	..	226	89.4	2.53	1.12	1.52	2	2.0
		7/20	+++	+++	161	1.70	..	210	82.7	2.54	1.21	1.52	3	2.3

average decrease of more than 10 per cent in the cardiac output per minute. Improvement was definite in one, questionable in two and absent in one. Thirteen patients showed changes of less than 10 per cent in the average cardiac output following the administration of digitalis. Benefit was distinct in five of these, questionable in seven and absent in one. The output of the heart in proportion to the oxygen consumption of the body was increased after digitalis therapy in eight patients, beneficial effects being definite in two, questionable in four and not evident in two. The cardiac output was diminished in proportion to the metabolism in three subjects following digitalis therapy. Of these, one patient showed definite improvement and two were questionably better. The cardiac output was unchanged (i.e., changed by 10 per cent or less) in relation to the metabolism in eleven subjects. Definite improvement was noted in five, a questionably beneficial effect in five and no effect in one. The means of all the average values for the cardiac output and the arteriovenous oxygen difference were as follows: The cardiac output was 2.82 liters before the administration of digitalis and 2.81 liters after therapy. The arteriovenous oxygen difference was 87.1 cc. per liter of blood before the administration of digitalis and 83.7 cc. after digitalis therapy. We interpret the findings as indicating that digitalis has no consistent effect on the cardiac output of persons with congestive heart failure.

This conclusion is different from that arrived at by Stewart and Cohn.[10] The disagreement can probably be attributed to the difference in the method employed for determining the cardiac output. Stewart and Cohn stated that their initial samples of gas were taken after fifteen seconds of rebreathing. In a previous study [18] it has been shown that such a short time does not usually suffice to obtain a homogeneous mixture in the lung-bag system for patients with congestive heart failure. Of the eight patients studied by the hydrogen method by Grollman, Friedman, Clark and Harrison,[18] an adequate mixture was obtained before twenty seconds of rebreathing in only two.

In an attempt to understand the difference between our results and those of Stewart and Cohn, we have made a number of measurements of the arteriovenous oxygen difference as determined according to the older technic with two samples used by them and according to the method requiring three samples, employed in the present study. Illustrative data are given in table 4. Ten such comparisons were made. In three instances false low results for the arteriovenous oxygen difference and false high results for the cardiac output were obtained when the samples were taken prematurely. In the remaining instances, too early sampling resulted in false high values for the arteriovenous oxygen difference and erroneously low values for the cardiac output. Furthermore, as illustrated by the first pairs of observations in table 4, agreement between

the results is not an adequate criterion of accuracy, as the arteriovenous oxygen difference obtained on successive rebreathings may agree and yet not be seriously inaccurate. Thus, when the samples are taken before a homogeneous mixture has been obtained in the lung-bag system, erroneous values for the arteriovenous oxygen difference and for the cardiac output are likely to be obtained. These observations seem to explain the discrepancy between our findings and those of Stewart and Cohn.

COMMENT

In some patients clinical improvement following the administration of digitalis is accompanied by an increase in the cardiac output. This

TABLE 4.—*Measurements of the Arteriovenous Oxygen Difference and Cardiac Output According to the Methods Employing Two Samples and Three Samples*

	Erroneous Data			Correct Data			
					Arteriovenous Oxygen Difference, Cc. per Liter		
Comment	Time of Samples, Seconds	Arteriovenous Oxygen Difference, Cc. per Liter	Cardiac Ouput per Minute, Liters	Time of Samples, Seconds	First	Second	Cardiac Output per Minute, Liters
	15-19	81	2.9	18-21-25	59	63	3.9
	16-19	72	3.3				
	17-21	118	2.1	23-28-33	102	96	2.5
	17-21	125	2.0				
Samples taken too soon giving inadequate mixture	17-21	166	1.8	21-26-31	97	94	3.1
	18-22	92	2.6	22-26-30	77	79	3.1
	19-24	94	1.6	24-28-32	77	71	2.1
	19-23	103	2.4	21-26-31	84	84	2.8
	18-24	108	2.2	20-25-30	93	87	2.7
	19-21	69	3.8	22-27-32	86	94	2.9
	20-24	82	2.5	24-28-32	107	100	2.0
	18-24	70	2.8	24-29-33	86	84	2.3

effect is probably due to the drug's action on the heart, for there is ample evidence from studies on the isolated heart and on the heart-lung preparation that the drug may under certain conditions increase the contractile power of the myocardium.

In other patients clinical improvement brought about by digitalis is associated with a decrease in the cardiac output per minute. Since such an effect is not usually observed in the isolated heart, it is reasonable to ascribe it to an action on the periphery, and there is much evidence in favor of such an assumption. Thus Dock and Tainter [8] found that the decline in the cardiac output produced in normal dogs by digitalis was associated with, and apparently due to, a decrease in the venous pressure. Stewart and Cohn [10] failed to find diminution in the venous pressure in normal persons and concluded that the diminished output was secondary to the decrease in the size of the heart. However,

Rytand [22] has recently studied a larger group of subjects, and his work indicates that the drug does diminish the venous pressure of normal persons. It seems probable, therefore, that the decrease in cardiac output which occurred in several of our patients was due to a peripheral action of digitalis. Just how this is brought about is still questionable. Dock and Tainter [8] found that the drug produced pooling of the blood in the portal system in experimental animals. The observations of Wollheim,[23] Schürmeyer [24] and Mies [25] indicated that digitalis causes diminution in the circulating blood volume not only in persons with cardiac disease but also in normal persons and in normal animals.

Many of our patients exhibited clinical improvement following digitalis therapy without showing a change in the cardiac output. It seems probable that in such instances the peripheral effect of the drug (tending to decrease the venous return) was balanced by the cardiac action (tending to increase the output). In any case, the results indicate that clinical improvement produced by digitalis cannot in general be ascribed to an increase in the blood supply to the tissues.

The one constant effect of digitalis on which all investigators have agreed, and which occurs in the isolated heart, in the heart-lung preparation, in normal animals, in animals with cardiac disorders, normal human beings and in human beings with congestive heart failure, is a diminution in the size of the heart. Congestive failure is invariably associated with dilatation, which leads to an increase in the venous pressure, and improvement is accompanied by a diminution in the degree of dilatation and by a fall in the venous pressure. As has been shown by Starling and Visscher,[26] the dilated heart is inefficient because it consumes more oxygen than does the normal organ in order to do a given amount of work. By enabling the heart to carry out its work with a smaller volume, i.e., by increasing the "fitness" and diminishing dilatation, digitalis increases cardiac efficiency. It seems probable that the heart is therefore able to perform the same amount of work with a smaller expenditure of energy and that this is the most important effect of digitalis. In patients with auricular fibrillation the diminution in heart rate and the elimination of pulse deficit after the administration of digitalis are of great importance, but these effects are often not apparent in persons with

22. Rytand, D. A.: The Effect of Digitalis on the Venous Pressure of Normal Individuals, J. Clin. Investigation **12**:847, 1933.

23. Wollheim, E.: Kompensation und Dekompensation des Kreislaufs, Klin. Wchnschr. **7**:1261, 1928.

24. Schürmeyer, A.: Ueber Blutmengenbestimmungen bei Herzfehlern, Verhandl. d. deutsch. Gesellsch. f. inn. Med., 1928, p. 388.

25. Mies, H.: Ueber die Wirkung des Strophanthin auf die zirkulierende Blutmenge, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1931, p. 208.

26. Starling, E. H., and Visscher, M.: The Regulation of the Energy Output of the Heart, J. Physiol. **62**:243, 1922.

regular rhythm. The increase in cardiac output after digitalis therapy may be of importance if the output has been previously markedly decreased, as occurs in certain patients with auricular fibrillation of sudden onset. In other cases, in which congestive failure occurs with a relatively normal output, the diminution of output following the administration of digitalis will tend to lessen the burden on the overloaded heart. However, since the most constant effect of the drug is on the size of the heart, it appears that benefit produced by it is to be ascribed in general to diminished dilatation, diminished expenditure of energy and increased efficiency.

SUMMARY

The effect of digitalis on the cardiac output of patients with congestive heart failure has been investigated by the acetylene method. Prior to the administration of digitalis, most of the subjects had subnormal values for the cardiac output.

Of twenty-two patients, three showed no improvement after the administration of the drug, ten had subjective benefit and eight exhibited definite objective improvement. In each of the groups some of the patients showed an increase in the cardiac output per minute, some a decrease and some no change. Consistent alterations of the cardiac output in proportion to the oxygen consumption were not observed.

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART III

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SECONDARY PULMONARY VASCULAR SCLEROSIS

DISTRIBUTION OF SCLEROSIS IN THE PULMONARY VASCULAR BED

It now seems desirable to discuss the distribution of sclerosis in the pulmonary vascular bed in the various etiologic groups. Tables 22 and 23 and figures 9 to 16 summarize the data obtained by averaging the degree of sclerosis noted in each etiologic group in the various divisions of the pulmonary vascular bed. Though this may be of some value in making a comparison of the various groups, it must be emphasized that since the grading of the sclerosis was according to arbitrary criteria, which necessarily differed with each type of vessel examined, the tables and figures show only in a general way the variations noted in the degree of sclerosis in the different divisions of the pulmonary vascular bed.

In the "no cause" group there were, if the case of primary sclerosis in a boy of 11 years is omitted, 15 cases in patients under 40, most of whom died of some acute infection. Sclerosis of some portion of the pulmonary vascular bed was present in all but 3. It was least frequent in the stem of the pulmonary artery and in the large veins and commonest in the large elastic arteries, arterioles, venules and small veins. Figure 9 shows that the average degree of sclerosis was small in all the divisions of the pulmonary vascular bed. The average curve did not differ markedly from the curves constructed for the individual cases in this group and so may be accepted as roughly indicating the distribution of sclerosis in the pulmonary vascular bed in the cases in this group.

All the patients over 40, even in the absence of factors known to raise the pulmonary arterial pressure, showed sclerosis of some portion of the pulmonary vascular bed. The distribution was similar to that

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In this series of five papers the superior numbers refer to the bibliography which will be published in connection with the last paper. The superior letters refer to footnotes.

TABLE 22.—*Distribution of Sclerosis in the Pulmonary Vascular Bed in Patients Less Than 40 Years of Age* *

Etiologic Factor	Number of Patients†	Stem of Pulmonary Artery			Large Elastic Arteries			Small Muscular Arteries			Arterioles and Venules			Small Veins			Large Intrapulmonary Veins			Main Extrapulmonary Veins		
		Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis
No cause	15	3 1 lost	21	0.3+	10 1 lost	67	0.9+	8	53	0.6+	12	80	1.1+	10	67	0.9+	3 2 lost	23	0.2+	11 lost	50	0.5+
Pulmonary disease	6	4	67	1.0+	5	100	1.4+	6	100	1.8+	6	100	2.8+	5	83	2.0+	1 1 lost	20	0.2+	0 3 lost	...	.....
Cardiac disease	2	1	...	1.5+	2	...	3.0+	2	...	2.0+	2	...	3.0+	2	...	4.0+	2	...	3.5+	2	...	2.0+
Hypertension	3	1 1 lost	...	0.5+	2 1 lost	...	1.0+	2	...	1.0+	3	...	2.0+	2	...	1.7+	0	...	0	..	...	.....
Pulmonary and cardiac disease	3	2	...	1.3+	2	...	0.7+	3	...	1.7+	3	...	3.0+	3	...	1.7+	3	...	2.3+	2 1 lost	...	2.0+
Cardiac disease and hypertension	..	..	...	.....	..	...	.....	..	...	.....	..	...	.....	..	...	.....	..	...	.....	..	...	.....
Pulmonary and cardiac disease and hypertension	..	..	...	.....	..	...	.....	..	...	.....	..	...	.....	..	...	.....	..	...	.....	..	...	.....
Pulmonary disease and hypertension	..	..	...	.....	..	...	.....	..	...	.....	..	...	.....	..	...	.....	..	...	.....	..	...	.....

* This table shows the number of patients with sclerosis and the average degree of sclerosis in each type of vessel in each etiologic group.

† One patient with primary pulmonary vascular sclerosis is not included.

TABLE 23.—*Distribution of Sclerosis in the Pulmonary Vascular Bed in Patients Over 40 Years of Age* *

Etiologic Factor	Number of Patients	Stem of Pulmonary Artery			Large Elastic Arteries			Small Muscular Arteries			Arterioles and Venules			Small Veins			Large Intrapulmonary Veins			Main Extrapulmonary Veins		
		Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis	Number with Sclerosis	Percentage	Degree of Sclerosis
No cause	15	7 1 lost	50	0.6+	14	93	1.6+	14	93	1.6+	15	100	2.2+	15	100	1.6+	6	40	0.6+	2 9 lost	33	0.3+
Pulmonary disease	23	15 1 lost	68	0.8+	23	100	1.9+	23	100	2.2+	23	100	2.4+	23	100	2.3+	13 4 lost	68	1.1+	9 11 lost	75	1.2+
Cardiac disease	5	3	60	1.4+	5	100	1.4+	5	100	1.6+	5	100	1.6+	4	80	1.4+	2 2 lost	...	0.7+	1 4 lost	...	2.0+
Hypertension	6	3	50	0.7+	6	100	1.7+	6	100	2.0+	6	100	2.8+	6	100	1.8+	2	33	0.3+	1 4 lost	...	1.0+
Pulmonary and cardiac disease	10	8	80	1.4+	10	100	2.5+	9	90	2.4+	9	90	2.2+	9	90	2.1+	8	80	1.3+	3 7 lost	...	1.3+
Cardiac disease and hypertension	3	2	...	1.3+	3	...	2.0+	3	...	1.7+	3	...	2.3+	3	...	2.0+	1 1 lost	...	1.0+	1 2 lost	...	2.0+
Pulmonary and cardiac disease and hypertension	3	1	...	0.3+	3	...	2.3+	3	...	2.3+	3	...	2.3+	3	...	2.3+	1	...	0.3+	2 1 lost	...	1.5+
Pulmonary disease and hypertension	5	5	100	1.6+	5	100	1.8+	5	100	3.0+	5	100	2.4+	5	100	2.4+	3	60	0.8+	2 1 lost	...	1.5+
Congestive heart failure†	25	19	76	1.4+	24	96	2.2+	25	100	2.4+	24	96	2.4+	24	96	2.4+	14 1 lost	58	1.1+	9 14 lost	82	1.8+

* This table shows the number of patients in each etiologic group and the average degree of sclerosis in each division of the pulmonary vascular bed in each etiologic group.

† This group includes all the patients with congestive heart failure irrespective of age.

in the patients under 40, and the curve of average severity ran roughly parallel, though at a somewhat higher level (fig. 9). It thus seems that sclerosis increases in frequency and severity with age in all parts of the pulmonary vascular bed except the main extrapulmonary pulmonary veins.

The "pulmonary disease" group was comprised of 29 cases. Six patients were over, and 23 under, 40. Tables 22 and 23 and figure 10

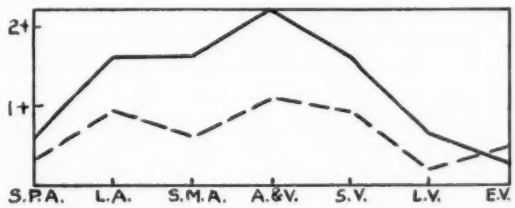

Fig. 9.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "no cause" group. In this chart and those that follow the dash line represents the patients under 40 and the solid line, the patients over 40 in the "no cause" group. S.P.A. indicates the stem of the pulmonary artery; L.A., large arteries; S.M.A., small muscular arteries; A.& V., arterioles and venules; S.V., small veins; L.V., large veins, and E.V., extrapulmonary veins.

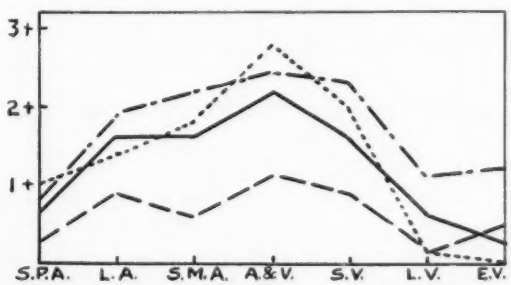

Fig. 10.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "pulmonary disease" group. The dotted line represents the patients under 40, and the dot-and-dash line, the patients over 40.

show the distribution and average severity of sclerosis throughout the pulmonary vascular bed in these cases. In all cases in patients under 40 sclerosis was present, and its average degree was greater than that in the corresponding cases in the "no cause" group except in the large intrapulmonary and extrapulmonary pulmonary veins. The marked sclerosis of the arterioles, venules and small veins was remarkable in view of the fact that the pressure in the veins might be expected, if anything, to be lower than normal. In all patients over 40 sclerosis was present in

some part of the pulmonary vascular bed. The curve of average severity ran parallel to and slightly above that in the cases of patients over 40 in the "no cause" group in all divisions of the pulmonary vascular bed, and the sclerosis was notably more severe than that in the "no cause" group in the large intrapulmonary and extrapulmonary pulmonary veins. The sclerosis reached its maximum, so far as the sclerosis in different portions of the pulmonary vascular bed could be compared, in the arterioles, venules and small veins.

The "cardiac disease" group was comprised of 7 cases. Two patients were under, and 5 were over, 40. Marked sclerosis was present throughout the pulmonary vascular bed in the patients under 40, both of whom died of congestive heart failure. The sclerosis was particularly marked in the venous portion of the pulmonary vascular

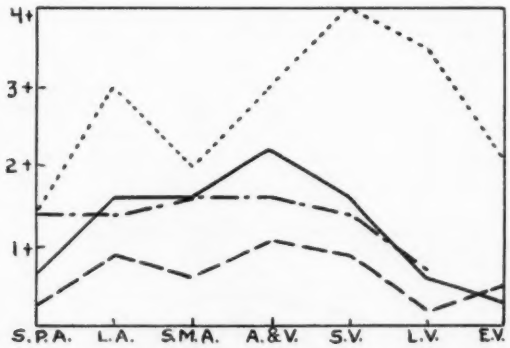

Fig. 11.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "cardiac disease" group. The dotted line represents the patients under 40, and the dot-and-dash line, the patients over 40.

bed and reached its maximum in the small veins, in which the average thickness of the walls was 25 per cent of the external diameter.

The 5 patients over 40 all had sclerosis of the coronary artery with cardiac hypertrophy but without heart failure. Figure 11 shows that the average degree of sclerosis was less than that in the "no cause" group in patients over 40 except in the stem of the pulmonary artery (there were not enough data as to the state of the extrapulmonary pulmonary veins); so it appears that cardiac disease without heart failure is not necessarily associated with a greater degree of sclerosis than may occur in otherwise normal elderly persons.

The "hypertension" group was comprised of 9 cases. Three patients were under, and 6 over, 40. All showed sclerosis in some part of the pulmonary vascular bed. Figure 12 shows that in the patients both

under and over 40 the degree of sclerosis was only slightly greater than that in the "no cause" group (except in the arterioles and venules and in patients under 40 in the small veins, where it was considerably greater), and that in the large veins it was, if anything, a little less than in the "no cause" group.

The "cardiac and pulmonary disease" group was comprised of 13 cases. Three patients were under, and 10 over, 40 (fig. 13). In

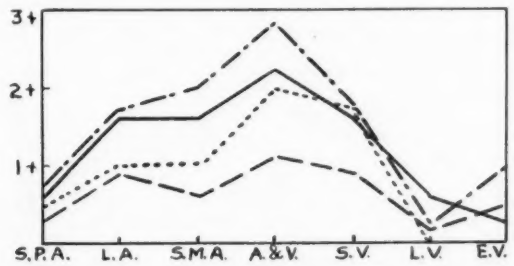

Fig. 12.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "hypertension" group. The dotted line represents the patients under 40, and the dot-and-dash line, the patients over 40 in the "hypertension" group.

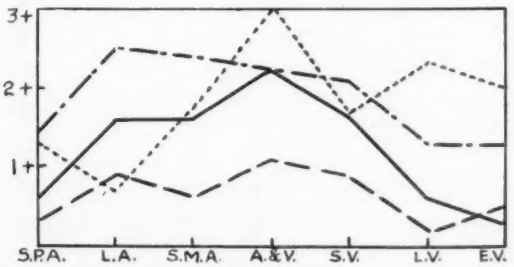

Fig. 13.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "pulmonary and cardiac disease" group. The dotted line represents the patients under 40, and the dot-and-dash line, the patients over 40.

those under 40 the average degree of sclerosis was slightly greater than that in the "no cause" group on the arterial, and considerably greater on the venous, side of the pulmonary vascular bed. Five of the 10 patients over 40 died of congestive heart failure. The general level of sclerosis was greater than that in the "no cause" group throughout the pulmonary vascular bed, on the arterial and venous sides, except in the arterioles and venules, where the sclerosis was the same as in

the "no cause" group. This group was remarkable for the relatively high degree of sclerosis in the large elastic arteries.

The "cardiac disease and hypertension" group consisted of 3 cases, all in patients over 40. Congestive heart failure was present in all. Figure 14 shows that the average degree of sclerosis was somewhat greater than in the "no cause" group in all parts of the pulmonary vascular bed.

The "cardiac and pulmonary disease and hypertension" group consisted of 3 cases. Two of the patients showed congestive heart failure. The average degree of sclerosis (fig. 15) was somewhat greater than

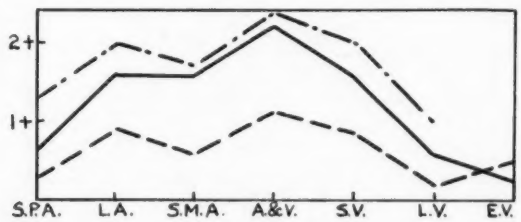

Fig. 14.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "cardiac disease and hypertension" group. The dot-and-dash line represents the patients over 40.

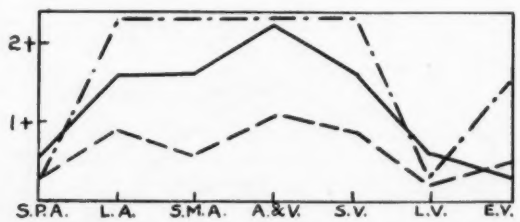

Fig. 15.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "pulmonary and cardiac disease and hypertension" group. The dot-and-dash line represents the patients over 40.

in the "no cause" group in all portions of the pulmonary vascular bed except the stem of the pulmonary artery and the large intrapulmonary veins, and the difference between the two etiologic groups was especially marked in the main extrapulmonary pulmonary veins.

The "pulmonary disease and hypertension" group consisted of 5 cases, all in patients over 40. Sclerosis was present in some part of the pulmonary vascular bed in all. The average degree of sclerosis was greatest (fig. 16) in the small muscular arteries and was greater than in the "no cause" group in all divisions of the pulmonary vascular bed,

particularly in the small muscular arteries and the extrapulmonary pulmonary veins.

Table 23 and figure 17 show the distribution and degree of sclerosis in the 25 patients of all ages with congestive heart failure. The average degree of sclerosis was greater than that in the "no cause" group in each division of the pulmonary vascular bed, particularly in the veins, large and small, but in each portion of the pulmonary vascular bed the changes were more severe in some one etiologic group than in the cases of congestive heart failure.

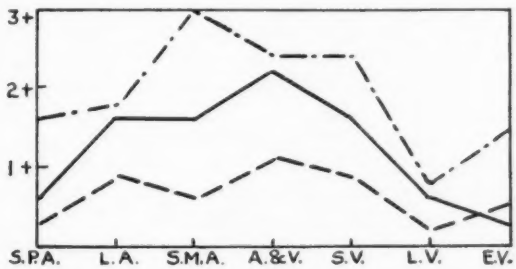

Fig. 16.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "pulmonary disease and hypertension" group. The dot-and-dash line represents the patients over 40.

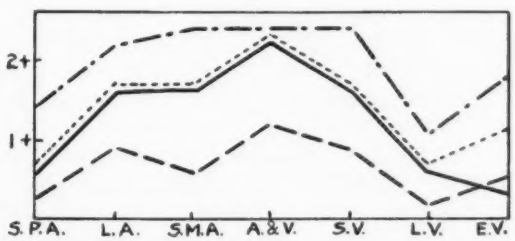

Fig. 17.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "congestive heart failure" group. The dot-and-dash line represents all the patients with heart failure, and the dotted line, all the patients without heart failure.

Thus, sclerosis increased in frequency and severity with increasing age in all divisions of the pulmonary vascular bed except the main extrapulmonary pulmonary veins, even in the absence of factors which are thought to raise the pulmonary venous pressure. The presence of such factors was associated with a slightly increased severity of sclerosis in all divisions of the pulmonary vascular bed, including the veins in the "pulmonary disease" group, in which it might be expected that the

blood pressure in the pulmonary veins would be low. The sclerosis was usually most marked in the arterioles, venules and small veins. In the various etiologic groups including cases of congestive heart failure and in the cases of congestive heart failure that have been reported, there was an especially heavy incidence of sclerosis on the venous side of the pulmonary vascular bed.

CHANGES IN THE HEART

Since there is no means of ascertaining the pulmonary blood pressure in man, the thickness of the right ventricle may be taken as a rough index, though it must be remembered that incompetence of the tricuspid valve as well as hypertension of the pulmonary vessels may cause hypertrophy of the right ventricle, and that, as in the systemic circulation, the degree of hypertrophy is not necessarily proportionate to the degree of hypertension. Hypertrophy of the right ventricle also occurs for unknown reasons (e. g., in cases of systemic hypertension or aortic incompetence, without evidence of heart failure [171]), and Lewis [171] has stated that ventricular hypertrophy must not be taken as certain evidence of excessive work on the part of the ventricle. Nevertheless, the thickness of the right ventricle is the only available index of overstrain of the right ventricle, and it has been used with a full realization of the necessary limitations. In view of these limitations it was not thought necessary to undertake the task of separating the ventricles and weighing them independently. It was thought sufficient merely to measure the thickness of the ventricular walls and to pay no attention to the degree of dilatation of the cavity. A thickness up to 4 mm. was considered normal, from 4 to 6 mm. moderate hypertrophy and over 6 mm. great hypertrophy.

In most of the cases of pulmonary arteriosclerosis reported in the literature the right ventricle was hypertrophied, either with or without dilatation,[x] or merely dilated or enlarged.[y] This was probably because only isolated cases have usually been reported, with unexplained congestive heart failure or hypertrophy of the right ventricle, and the pulmonary arteries have been examined to find an explanation. Kisch [147] carefully examined 25 hearts showing hypertrophy of the right ventricle taken from patients who had had chronic pulmonary disease and other diseases but no independent cardiac disease or systemic hypertension. He weighed the ventricles separately and measured their thickness and the volume of the cavities. In 10 cases only the right ventricle and in 15 the whole right side of the heart was hypertrophied. None of the first group and all of the second showed chronic venous con-

(*x*) 47, 102, 106, 113, 174, 193, 202, 204, 226, 252, 262, 276, 288, 308, 331.

(*y*) 182, 186, 250, 262.

gestion in the systemic circulation. The left ventricle was hypertrophied in none of the first group and in 4 of the second. This he attributed to transmission of the venous hypertension back through the capillaries to the systemic arteries, but that appears unlikely; at all events it should have caused systemic hypertension, but with the exception of a blood pressure of 160 in 1 patient hypertension was absent. The right ventricle was dilated in 5 patients in the first and 14 in the second group. At first only the "outflow path" is hypertrophied and dilated (i. e., from the apex of the right ventricle to the orifice of the pulmonary artery). Later the "inflow path," from the tricuspid orifice to the apex of the right ventricle, also dilates and hypertrophies. Usually, even when there was hypertrophy of the right auricle, there was no dilatation of the tricuspid valve, but the pulmonary orifice was dilated in 11 of the 25 cases.

In many of Giroux's [114] cases of pulmonary tuberculosis with pulmonary arteriosclerosis there was no hypertrophy of the right ventricle. Boas [34] noted in 97 cases of pulmonary tuberculosis that the electrocardiogram showed preponderance of the right ventricle in 29 per cent and preponderance of the left ventricle in 30 per cent. Preponderance of the right ventricle was found chiefly in the younger patients, and there was no excessive tendency of the patients with fibrosis of the lungs to show this preponderance. Dubrow [83] noted after thoracoplasty in dogs that the T wave in lead III tended to become negative (which he interpreted as evidence of strain on the right ventricle) and that at autopsy the right ventricle contained more fat than normal.

In the present series the right ventricle was normally thick in 53 cases, moderately thickened in 35 and greatly thickened in 10. In 2 cases the thickness was not recorded. Age and sex made no difference. Tables 24 and 25 show the relationship of the etiologic factors to the thickness of the right ventricle. The "no cause" group contained the largest proportion of cases in which the right ventricle was normal, but it also contained 2 cases (7 per cent), including that of the boy of 11 with primary pulmonary vascular sclerosis, in which there was great hypertrophy of the right ventricle. The right ventricle was normal least frequently in the "cardiac disease," "hypertension," "cardiac and pulmonary disease" and "pulmonary and cardiac disease and hypertension" groups, and it was greatly thickened most frequently in the same groups. Table 25, which gives analyses of the etiologic groups, shows that pleural adhesions and pulmonary abscess were not associated with hypertrophy of the right ventricle, while in cases of cardiac disease hypertrophy of the right ventricle was least common in cases of sclerosis of the coronary artery without congestive heart failure and was most common in cases of rheumatic cardiac disease and syphilitic aortitis. The frequency of great hypertrophy of the right ventricle in

cases of systemic hypertension is noteworthy and has been commented on by others.[z] The cause is not clear. The hypertrophy may occur

TABLE 24.—*Relationship of the Thickness of the Right Ventricle to the Etiologic Factor*

Etiologic Factor	Number of Patients	Patients with a Normal Right Ventricle (up to 4 Mm.)		Patients with a Moderately Thickened Right Ventricle (Between 4 and 6 Mm.)		Patients with a Greatly Thickened Right Ventricle (Over 6 Mm.)	
		Number	Percentage	Number	Percentage	Number	Percentage
No cause	30	24	80	4	13	2	7
Pulmonary disease	29	18	62	11	38	..	..
Cardiac disease	7	2	29	3	43	2	29
Hypertension	9	1	11	5	56	3	33
Pulmonary and cardiac disease	12	4	33	6	50	2	17
Cardiac disease and hypertension	3	..	..	3	100	..	..
Pulmonary and cardiac disease and hypertension	3	1	33	1	33	1	33
Pulmonary disease and hypertension	5	3	60	2	40	..	..

TABLE 25.—*Further Analysis of the Relationship of the Etiologic Factor to the Thickness of the Right Ventricle*

	Etiologic Factor	Number of Patients	Normal Right Ventricle		Moderately Thickened Right Ventricle		Greatly Thickened Right Ventricle	
			Number	Percentage	Number	Percentage	Number	Percentage
A. Pulmonary disease (isolated or combined with cardiac disease or hypertension)	Bronchitis alone	1	..	..	1	..	..	..
	Emphysema alone	26	14	54	10	38	2	7
	Fibrosis of lungs	4	3	..	1	..	..	..
	Emphysema and fibrosis	12	5	42	6	50	1	8
	Abscess	4	4	100	..	..	..	..
B. Pleural adhesions (in patients in "no cause" group)	No adhesions	16	13	81	1	6	2	13
	Patchy adhesions	11	8	73	3	27	..	..
	Patchy adhesions on one side; universally adherent on the other	1	1	..	..	..	..	..
	Both pleurae obliterated	..	..	..	..	..	..	..
C. Heart disease (alone or combined with pulmonary disease or hypertension)	Rheumatic with mitral disease	2	..	..	1	..	1	..
	Rheumatic, mitral and aortic disease	3	1	..	1	..	1	..
	Aortic stenosis (isolated)	1	..	..	..	..	1	..
	Coronary arteriosclerosis with cardiac hypertrophy	16	6	38	7	43	3	19
	Syphilitic	9	2	22	5	56	2	22
	Idiopathic hypertrophy	1	..	..	1	..	..	..
	Pericarditis	1	..	..	1	..	..	..

without congestive heart failure. It has been attributed to an increased blood flow in the coronary artery. Possibly there is a simultaneous

(*z*) 17, 1, 176.

hypertension of the pulmonary vessels due to the same cause as the systemic hypertension.

Table 26 and figure 18 show that while in general the greater the thickness of the right ventricle the greater the sclerosis throughout the pulmonary vascular bed, the difference was slight and did not hold for all portions of the pulmonary vascular bed. Moreover, the table and figure represent average figures, and the correspondence in individual cases was even less close. It must therefore be concluded either that the thickness of the right ventricle is an imperfect guide to the

TABLE 26.—*Relationship of the Degree of Sclerosis in the Pulmonary Vascular Bed to the Thickness of the Right Ventricle*

Thickness of Right Ventricle	Number of Patients	Stem of Pulmonary Artery	Large Elastic Arteries	Small Muscular Arteries	Arterioles and Venules	Small Veins	Large Veins	Extrapulmonary Pulmonary Veins
Normal	53	0.7+	1.6+	1.8+	2.0+	1.8+	1.0+	1.1+
Moderately thickened	35	0.9+	1.9+	1.9+	2.4+	1.9+	0.8+	1.2+
Greatly thickened	10	1.2+	2.2+	2.0+	2.1+	2.0+	1.4+	1.5+

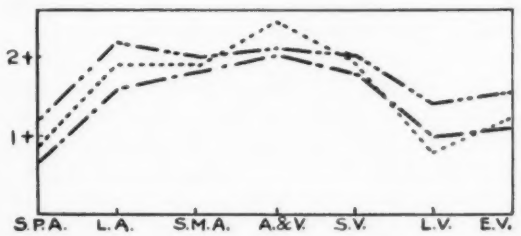

Fig. 18.—Graph showing the relationship of the degree of thickness of the right ventricle to the degree of sclerosis in the pulmonary vascular bed. The dot-and-dash line represents normal thickness; the dotted line, moderate thickness, and the two-dots-and-dash line, great thickness, of the right ventricle.

height of the pulmonary arterial pressure or that a raised pulmonary arterial pressure is not the only cause of pulmonary vascular sclerosis.

ETIOLOGY OF SECONDARY PULMONARY VASCULAR SCLEROSIS

The bearing of the facts previously discussed on the pathogenesis of pulmonary arteriosclerosis will now be considered. This must be done in connection with the question of the pathogenesis of arteriosclerosis in general. Attempts to isolate the problem of pulmonary arteriosclerosis must inevitably fail.

1. *Age.*—In elderly persons systemic arteriosclerosis is practically constant. Wells [321] said that in old age the colloids of the elastic fibers of the aortic media lose water and become less dispersed and more

granular. Aschoff [14] said that products of wear and tear accumulate and are precipitated and that an increase in the fibrous tissue in the intima and media normally occurs. Therefore, the arteries of the aged normally become rigid, inelastic, elongated, dilated and tortuous. Many writers [a] have said that this is an important predisposing cause of sclerosis. The blood stream is slowed in the dilated arteries, and this, in some unspecified manner (Thoma), causes proliferation of the intimal elastic tissue, which tends to restore the lumen to its original size and the blood flow to its original velocity. This teleologic theory does not account for the many cases in which sclerosis not only restores the lumen to normal but narrows it almost to the point of obliteration. In the present state of knowledge it is probably best to ascribe senile arteriosclerosis to the "wear and tear of a long life," a phrase which at least has the merit of being broad enough to cover any information which may be gained in the future.

Most of the few observers who have studied sclerosis in the pulmonary circulation have agreed that it increases with age. Fischer [103] expressed the belief that it is due to the presence of senile emphysema, but no one else has agreed with him. Ljungdahl [176] observed macroscopic sclerosis in 50 per cent of 52 patients over 50 with no condition likely to raise the pulmonary blood pressure, and microscopic sclerosis in 58 per cent. Wartman [312] noted in routine sections made in 426 consecutive autopsies that slight sclerosis was present in 6.4 per cent of males under 30 and slight sclerosis in 8.6 per cent and severe sclerosis in 2.9 per cent of females, while in persons over 60 slight sclerosis was present in 41.6 per cent of males and 22.2 per cent of females and severe sclerosis in 16.9 per cent of males and 17.5 per cent of females.

In the present series the influence of age is shown in figure 9 and tables 4 to 23. Excluding 1 patient with primary sclerosis, there were 15 patients under 40 and 15 over 40 in whom there was no reason to expect a raised pressure in the pulmonary vessels. Slight sclerosis was present in all portions of the pulmonary vascular bed in most of the patients under 40 (except in the stem of the pulmonary artery and the large veins, which were only occasionally involved); sclerosis was present in every patient over 40 and was usually more severe in every portion of the pulmonary vascular bed. The fact that sclerosis is so common in youth shows that age per se is not the cause; but the fact that it is commoner and more severe in later life suggests that it is due to some factor or factors which act continuously or at intervals throughout life, so that exposure to these factors increases with age.

2. *Changes in the Vasa Vasorum.*—Such changes have been held responsible, though this theory is unlikely because the vasa vasorum

(*a*) 237, 321.

supply only the outer third of the media, the inner two-thirds and all the intima being supplied from the lumen of the vessel. Posselt [240] suggested that in cases of mitral stenosis the pulmonary artery is stretched and that there are narrowing of the vasa, atrophy of the tissue supplied by them and secondary sclerosis of the overlying intima. Mair [193] suggested that in his case the sclerosis may have been secondary to sclerosis of the bronchial vessels, from which the vasa are derived. In the present series the bronchial arteries and vasa vasorum often showed sclerosis, but no relationship could be traced to the sclerosis of the pulmonary vessels. In view of the lack of evidence that systemic arteriosclerosis is due to disease of the vasa, it must be concluded that pulmonary vascular sclerosis is not due to sclerosis of the bronchial arteries or of the vasa vasorum.

3. *Infection.*—Most observers have found no evidence that infection causes arteriosclerosis.[b] Some [c] have expressed the belief that infection possibly may act indirectly by disturbing the cholesterol metabolism or vasomotor tone. Others [d] have said that infection is important. Posselt [240] said that 3 of his own 10 patients had smallpox in their youth. Some writers [e] have contended that in cases of mitral stenosis infection, probably rheumatic, as well as hypertension of the pulmonary vessels is important in causing the sclerosis. In two instances Zeek [332] observed pulmonary arteriosclerosis in the stillborn fetus of a septic mother. Wiesel [f] described edema and necrosis followed by fibrosis in the media of systemic and pulmonary vessels in cases of infection and considered that these predispose to true arteriosclerosis. It should be noted that the changes described by Wiesel were not those of arteriosclerosis and that the evidence of others depended on insufficient statistical material or erroneous interpretation of histologic appearances. In the present series no correlation between infection and the occurrence of arteriosclerosis could be made out, and it would be difficult to prove that any connection existed, since both pulmonary arteriosclerosis and infection in the past history were almost universally present. The histologic changes were those of a degenerative, not an inflammatory, lesion from the earliest stages at which they could be recognized. The only point favoring the theory of a connection with infection was that sometimes the changes were most marked near local changes in the lungs, such as chronic abscesses, foci of tuberculosis and patches of fibrosis.

(*b*) 138, 176, 188, 213.

(*c*) 14, 138.

(*d*) 96, 161, 186, 240, 295, 324, 325, 331, 332, 333.

(*e*) 161, 295, 304.

(*f*) 324, 325.

4. *Poisons.*—Poisons, such as alcohol, tobacco and lead, have been blamed.[g] Aschoff suggested that they may act by causing changes in the metabolism or in the vasomotor tone. Kitamura described a case of pulmonary arteriosclerosis in a patient who drank beer excessively, but attributed the sclerosis to plethora rather than to the toxic effects of alcohol. Macnider gave rabbits 50 cc. of a 20 per cent solution of alcohol daily and noted that in 9 of the 13 animals intimal lesions developed that resembled atherosclerosis, together with round cell infiltration of the media, but that similar lesions were present in 3 of the 16 controls. Thus, there is no good evidence that arteriosclerosis in general or pulmonary arteriosclerosis in particular is due to the action of toxins.

5. *Hormones.*—Anitschkow [6] said that castration and thyroidectomy facilitate the experimental production of atheroma by means of diet containing cholesterol, while the administration of thyroid makes it more difficult. Aschoff [14] suggested that the lipemia of diabetes and the hypocalcemia of tetany may play a part. Systemic arteriosclerosis is common in cases of diabetes, but Ljungdahl [176] observed pulmonary arteriosclerosis in only 1 of 6 young diabetic patients.

6. *Nervous Influences.*—Harris [126] observed that section of the cervical portion of the sympathetic trunk in rabbits caused endarteritis obliterans of the arteries of the ear, fragmentation of the elastica and hyperplasia of the media followed by patchy atrophy and fibrosis. Shaw [279] reported that irritation of the cervical vagus and sympathetic nerves caused aortic atheroma in 20 of 25 rabbits. Similar lesions were present in only 1 of 22 controls. Stopford [291] said that continuous irritation of the brachial plexus by a cervical rib causes intense spasms of the arteries of the limb and of their vasa vasorum, which result in intimal thickening, patchy endothelial destruction and thrombosis with organization and recanalization. However, there is no sufficient evidence that such processes play a part in the production of the ordinary systemic or pulmonary arteriosclerosis.

7. *Direct Irritation of the Vessels.*—In some of Brüning's [48] cases particles of coal dust were present in the walls of some of the sclerotic vessels. In Rosenthal's [256] cases of pneumonoconiosis it was suggested that the dust particles destroyed many pulmonary capillaries and initiated the arterial changes. In Macaigne's [180] case fungus filaments grew into the arterial walls and appeared to initiate the *thrombo-artérite.* Such factors can rarely, if ever, be the cause of pulmonary arteriosclerosis.

(*g*) 14, 63, 148, 176, 191, 295.

8. *Cholesterol Metabolism.*—In rabbits fed cholesterol Anitschkow noted deposits of cholesterol in the aortic intima, at the origin of branches and other sites characteristic of natural atheroma, and in the pulmonary artery and great veins. If the cholesterol feeding was stopped, the intimal cholesterol gradually disappeared, but thickened fibrous patches were left. Clarkson [58] observed that feeding rabbits on a diet with a high protein and low fat content produced atheroma, and that the rabbits showed evidence of hypercholesterolemia. Aschoff [h] expressed the belief that the primary change is the infiltration into the intima of lipoid-containing plasma and the deposition of cholesterol. In children but not in adults the lipoid may be reabsorbed. The lipoid content of the diet does not affect the occurrence of atheroma but determines the amount of cholesterol in the plaques. Roger [253] said that the pulmonary arterioles are especially concerned in fat metabolism, so that they should be particularly prone to be arteriosclerotic. Any fat that is liberated into the systemic circulation (e. g., after a fatty meal) tends to be arrested in the pulmonary arterioles, where it is absorbed and destroyed by the endothelial cells. MacMahon [190] reported a case of alcoholic fatty liver, with hepatic destruction due to carbon tetrachloride poisoning and liberation of the fat into the blood. At autopsy the blood of the right side of the heart and pulmonary arteries contained a great deal of fat, which rose to the surface on standing, while that of the pulmonary veins and left side of the heart contained none. The earliest histologic change is the deposition of cholesterol in the intima, followed by connective tissue proliferation superficial to this.

There is thus no doubt as to the importance of the deposition of cholesterol, though whether it is primary or secondary has not been determined. Roger's work suggested that the pulmonary vessels are particularly closely concerned in lipoid metabolism, but it should be noted that atheroma has thus far been produced by cholesterol feeding only in herbivorous animals on a diet foreign to them.

9. *Constitutional Inferiority.*—A constitutional inferiority of the material of which the arteries are composed has been suggested as a cause of marked pulmonary arteriosclerosis in the absence of factors likely to raise the pulmonary arterial pressure markedly, a suggestion which can be neither proved nor disproved, though Posselt [240] said that the small left ventricle, hypoplastic aorta and narrow pulmonary veins seen in some cases of pulmonary vascular sclerosis indicate the poor quality of the vascular system and Wätjen [308] described sinus-like dilatations of the pulmonary arteries in his case of vascular sclerosis in an infant of 11 months with congenital cardiac disease. There is thus

(*h*) 13, 14.

little evidence that inferiority of the "vital rubber" is a factor, and even if it were, this explanation could not be thought satisfactory until it had been shown in what the inferiority consists.

10. *Pulmonary Vascular Hypertension.*—This is thought by most to be the chief factor, but chiefly because pulmonary vascular sclerosis is rarely looked for in cases in which there is no mitral stenosis, etc. Steinberg [284] noted gross sclerosis in 62 per cent of cases in which there was no obstruction to the pulmonary circulation and in 82 per cent of cases in which there was obstruction (mitral stenosis, emphysema, etc.). Moschowitz [1] expressed the belief that pulmonary arterial hypertension is the cause of the sclerosis and said that in cases of mitral stenosis the veins as well as the arteries are sclerotic, while in cases of emphysema, in which the obstruction is prevenous (in the capillaries), the veins do not show sclerosis—a statement with which it is impossible to agree. Evans [102] described a case of collapse of the right lung in which the vessels in the collapsed lung were normal while in the normal left lung there was marked arteriosclerosis. This he interpreted as indicating that collapse prevented the entry of an adequate amount of blood into the right lung, so that the pressure there was low. It is difficult to believe, however, that there could have been a significant difference in pressure in the two lungs, at least in the large vessels.

The influence of hypertension in the development of systemic arteriosclerosis is not clear. Allbutt [4] said that in more than 50 per cent of cases of arteriosclerosis the blood pressure is not raised, and that in cases of long-standing hypertension the arteries may be normal.

At this point it seems opportune to examine the various factors which are generally thought to raise the pulmonary blood pressure.

A. Chronic Pulmonary Disease: The following conditions are of interest: 1. Emphysema. The effect of emphysema on the blood flow through the lungs is doubtful, as indicated in the section on pathologic physiology, and in many cases the right ventricle is of normal thickness. The reserve of pulmonary capillaries is so great that probably only the most extreme emphysema increases the resistance to blood flow through the lungs. Alexander [8] noted evidences of preponderance of the right ventricle in the electrocardiograms of only 3 of 50 patients with long-standing asthma with emphysema, and 1 of these patients showed mitral stenosis also.

The importance of emphysema in producing pulmonary vascular sclerosis is disputed. Some [j] have stated that sclerosis is no commoner in patients with emphysema than in patients of the same age without emphysema. Fischer [103] said that sclerosis is always present in cases

(*i*) 212, 213, 214.
(*j*) 64, 176, 240, 331.

of emphysema and that sclerosis occurs in the aged only in the presence of emphysema. Steinberg [284] observed sclerosis in 86 per cent of patients with emphysema, as compared with 62 per cent of patients without pulmonary or cardiac disease. Again, some observers who have admitted the coexistence of emphysema and pulmonary vascular disease have stated that the arterial lesions are primary and that the emphysema is secondary, just as in cases of primary contracted kidney the renal lesions are secondary to the arterial lesions.[k]

2. Pulmonary fibrosis. The means by which pulmonary fibrosis may obstruct the pulmonary circulation are discussed in the section on pathologic physiology. It seems probable that only the most extreme fibrosis could be effective and that therefore it is doubtful whether pulmonary fibrosis is important in raising the pulmonary blood pressure.

3. Pleural adhesions. These have been thought to interfere with the respiratory movements and so to throw a strain on the right ventricle, but it is doubtful if this is important in causing pulmonary vascular sclerosis.

4. Pulmonary tuberculosis. This may act by the absorption of toxins or by causing pulmonary fibrosis, compensatory emphysema and pleural adhesions. There is little evidence, however, that it ever causes a marked rise in the pulmonary blood pressure or that it is important in the production of sclerosis.

5. Neoplasm. Fried [107] said that vessels near masses of growth often are thickened, either by tumor invasion or by degenerative changes. Rössle [252] described a case in which many arteries with deposits of growth in the perivascular lymphatic vessels showed marked sclerosis. Hornowski [130] and Lutembacher [182] each described a case in which a main pulmonary artery was narrowed by a mediastinal mass of growth, the right ventricle was hypertrophied, and the pulmonary vessels were sclerotic. This evidence is not enough to establish neoplasm or compression of the pulmonary artery as a cause of pulmonary vascular sclerosis.

6. Thoracic deformities. These are often said to be the cause of failure of the right heart and of pulmonary vascular sclerosis. Edeiken [91] said that in cases of kyphoscoliosis one lung is compressed and may be fibrosed while the other shows compensatory emphysema, which further embarrasses the heart. The respiratory movements are restricted, and the growth of the chest lags behind that of the rest of the body. The vital capacity is reduced by from 20 to 60 per cent. But in 26 cases of kyphoscoliosis he noted evidence of preponderance of the right ventricle in electrocardiograms only once. Ljungdahl [176] observed sclerosis

(*k*) 96, 193, 215.

in 4 or 5 cases of kyphoscoliosis. The theory as to the importance of thoracic deformities in raising the pulmonary blood pressure and causing pulmonary vascular sclerosis therefore needs further investigation before it can be accepted.

In the present series there were 29 cases of uncomplicated pulmonary disease (emphysema with or without fibrosis and chronic tuberculosis). Figure 10 and tables 22 and 23 show that in patients under 40 the sclerosis was greater in all portions of the pulmonary vascular bed (including the small veins), except the large veins, than in the "no cause" group, while in patients over 40 the sclerosis was greater in the veins as well as the arteries than in the "no cause" group. Since in cases of pulmonary disease the obstruction is in the capillaries, it might be expected that, even if the pulmonary arterial pressure is raised, the venous pressure would be lowered, so that it is difficult to accept a simple mechanical explanation for the sclerosis. It has been pointed out that in some cases in which there are localized lesions of the lung (chronic abscess, fibrocaseous tuberculosis or fibrosis) the vascular lesions may be confined to the neighborhood of the pulmonary lesions.

Thus it seems that only in extremely advanced cases of pulmonary disease is the pulmonary circulation likely to be seriously obstructed. Nevertheless, the present investigation confirms previous ones in showing an increased frequency and severity of pulmonary vascular sclerosis in the presence of chronic pulmonary disease, though the incidence even without pulmonary disease is so great as to make the interpretation difficult, and the fact that veins as well as arteries share in the increased sclerosis makes it impossible to accept increased blood pressure as the only cause.

B. Chronic Cardiac Disease: In cases of congestive heart failure the left side of the heart usually fails before the right side, and the pressure in the pulmonary vascular bed rises more in the veins than in the arteries, since distensibility of the capillaries prevents the full rise in pressure from being transmitted back to the arteries. Ljungdahl [176] said that pulmonary vascular sclerosis is always present in cases in which there is stasis in the pulmonary circulation. Costa [1] observed sclerosis in only 18 of 25 cases of mitral stenosis. Miller [203] observed sclerosis in only 15 of 52 cases of mitral stenosis, but his figures were obtained from routine autopsy notes and are therefore valueless. Zeek [332] observed sclerosis in 59 of 62 cases of rheumatic cardiac disease, and in 9 of these it was severe. Steinberg [284] observed gross sclerosis in 29 of 35 cases of mitral stenosis (83 per cent), and in only 1 of these (3 per cent) was it severe. He observed sclerosis in 88 per cent of 68 cases of cardiac disease of all varieties, compared with 62 per cent

(*1*) 63, 64.

of cases in which there was no obstruction to the pulmonary circulation. Pulmonary vascular sclerosis has also been described in types of congenital cardiac disease, such as patency of the ductus arteriosus or of the interventricular septum, in which the aortic pressure is transmitted to the pulmonary artery.[m] But Posselt [240] also noted that in 4 per cent of his cases of pulmonary sclerosis, pulmonary stenosis, which might be expected to lower the pulmonary vascular pressure, was present.

In the cases of patients over 40 in the present series (fig. 11 and tables 6 to 23) the sclerosis in the "cardiac disease" group (sclerosis of the coronary artery and cardiac hypertrophy without congestive heart failure) was no greater than in the "no cause" group, though sclerosis was present in some part of the pulmonary vascular bed in all cases. The 2 patients under 40 both died of congestive failure, and in these cases the sclerosis was much greater than in the "no cause" group, particularly on the venous side. Thus, cardiac disease per se does not influence the frequency and severity of pulmonary vascular sclerosis, but if congestive heart failure is present, the frequency and severity of the sclerosis are increased in all parts of the pulmonary vascular bed (fig. 17).

C. Systemic Hypertension: Probably a transient rise in the systemic blood pressure does not cause a mechanical rise of pulmonary vascular pressure (see section on pathologic physiology), but it is possible that in cases of permanent hypertension there may be a spasm of the pulmonary as well as of the systemic arterioles, and pulmonary vascular hypertension may thus be caused. However, this seems improbable, since it is unlikely that the contraction of the pulmonary arterioles is of great importance in regulating the pulmonary blood pressure. Nevertheless, in many patients with systemic hypertension, even without heart failure, the right ventricle as well as the left was hypertrophied (table 24). Tables 6 to 23 and figure 12 show that while in patients under 40 the sclerosis was greater in all divisions of the pulmonary vascular bed than in the "no cause" group (this was probably chiefly because the "no cause" group included many cases in children and the "hypertensive" group, none), there was comparatively little difference in patients over 40. The cause of the common hypertrophy of the right ventricle in cases of systemic hypertension thus remains unknown, and there is no evidence that systemic hypertension is a factor in causing pulmonary vascular sclerosis.

Thus, all that can be said with confidence is that pulmonary vascular sclerosis increases in frequency and severity with the age of the patient and that factors which raise the pulmonary vascular pressure somewhat increase the frequency and severity of sclerosis in both pul-

(*m*) 174, 176, 240, 308.

monary arteries and veins. Pulmonary vascular sclerosis is practically as common as systemic vascular sclerosis and is constant in patients over 40. It is this universality which makes it so difficult to point to any one specific cause, though, as with systemic arteriosclerosis, the importance of age and hypertension as accessory factors seems fairly clear.

SYMPTOMS

It is obviously extremely difficult to differentiate the symptoms of secondary pulmonary vascular sclerosis from those of chronic pulmonary or cardiac disease which it complicates. Nevertheless, a great deal that seems singularly uncritical has been written on the symptoms. In the present series of 100 consecutive cases sclerosis was present in 97. Circulatory symptoms were present during life in only 25, and in all except 1 (a most unusual case of primary pulmonary vascular sclerosis, to be described later) some other cause for the circulatory symptoms was present. It may therefore be said that there is no clear evidence that pulmonary vascular sclerosis usually gives rise to symptoms.

The clinical picture as depicted in the literature is as follows:

Onset.—Often the patient has had chronic bronchitis or asthma for many years. Then congestive heart failure characterized by dyspnea, cyanosis, edema and other symptoms, gradually appears and steadily progresses. In these cases the sclerosis is secondary to chronic pulmonary disease. In other cases either dyspnea or cyanosis is the first symptom, followed by other symptoms of congestive heart failure. In most of these cases the sclerosis is secondary to mitral stenosis. In three cases [n] the onset was after childbirth and the first symptom was edema of the legs.

Dyspnea.—Dyspnea, often severe and associated with orthopnea, was present in most of the cases reported. In some cases [o] dyspnea was slight or absent, and the authors said that dyspnea was strikingly slight as compared with the cyanosis—a statement that is not borne out by most of the published case reports. Some authors have attributed the dyspnea directly to the arterial lesions and have said that narrowing of the arteries causes a more rapid flow of blood through the lungs and therefore insufficient oxygenation of the blood, resulting in dyspnea. But oxygenation occurs in the capillaries, and narrowing of the arteries does not necessarily cause quickening of the flow through the capillaries. In any case the weight of the evidence favors the view that a reduction in the vital capacity is the chief cause of dyspnea, and it is difficult to see how the arterial changes could directly cause a diminution in the vital capacity.

(*n*) 47, 102, 262.

(*o*) 103, 106, 186, 239, 262.

Cyanosis.—Cyanosis as intense as that in cases of congenital cardiac disease is usually said to be an early symptom, though in some of the cases [p] reported it was slight or absent. Thomas [295] said that cyanosis does not occur until the roentgenogram shows evidence of pulmonary vascular hypertension (bulging of the pulmonary artery and of the conus of the right ventricle) and is usually not marked until venous stasis is superadded. Cyanosis has been attributed to narrowing of the pulmonary arteries and a consequently more rapid flow through the capillaries, but there is no reason that narrowing of the arteries should quicken the flow through the capillaries. Cyanosis has also been attributed to a diminution in the number of capillaries as a result of emphysema, pulmonary fibrosis and other conditions, with a reduction in the volume of oxygenated blood. A sufficient reduction in the number of capillaries may indeed reduce the flow of blood through the lungs and therefore the volume of blood oxygenated per minute, but if all else is normal, all the blood that flows through the lungs and reaches the systemic circulation would be fully oxygenated, so that cyanosis should not occur. The cyanosis is probably due to the fact that some blood flows through the lung tissue that is inaccessible to air because of fibrosis, edema, etc., so that it remains unoxygenated. It is unlikely that pulmonary vascular sclerosis per se has any influence.

Hemoptysis.—This was sometimes a prominent symptom, especially in cases of mitral stenosis, pulmonary tuberculosis and other chronic pulmonary infections. Infarcts were sometimes present. Pulmonary vascular sclerosis, though it has often been blamed, does not seem to be responsible.

Pain.—Pain of a pleural type may occur in cases of pulmonary infection or of pulmonary infarction. In addition, so-called hypercyanotic angina, or dyspragia intermittens angiosclerotica pulmonalis, has been described.[q] Posselt [239] said that Nothnagel observed pain in 18 per cent of cases of mitral stenosis. The attacks are produced by exertion or excitement. There is retrosternal pain radiating into the depths of the lungs and associated with an intensification of the cyanosis and sometimes with restlessness and anxiety. The pain is sometimes relieved by deep breathing. Posselt suggested that spasm of the small pulmonary vessels causes, in some unspecified way, an increase in the cyanosis and also a raised pressure in the pulmonary vessels, which stretches the sclerotic large arteries and so causes pain. This theory is entirely speculative. More probably the pain is a variety of ordinary angina. The cyanosis is associated with anoxemia of the myocardium as well as of other tissues, and perhaps during exertion this may increase

(*p*) 47, 174, 246, 262.
(*q*) 96, 239, 276, 288, 295, 304.

to the point at which pain is produced. Though many authors have said that hypercyanotic angina may occur, only a few cases have actually been described. The only case in the present series occurred in a boy of 11 with primary pulmonary vascular sclerosis and will be discussed in the appropriate section.

Mental Symptoms.—These occur occasionally, especially when there is intense cyanosis. The patient becomes increasingly drowsy and may fall asleep even while eating. Finally he relapses into a coma and dies. Loss of weight sometimes occurs, as in other forms of chronic cardiac disease, but it is not a leading symptom.

Clubbing of the Fingers.—This sometimes develops, especially in cases of chronic pulmonary disease, and possibly is to be attributed to this and the chronic cyanosis rather than to the pulmonary vascular sclerosis.

Physical Signs in the Lungs.—There may be the signs of disease of the lungs to which the sclerosis is secondary (such as emphysema, pulmonary fibrosis, bronchiectasis and tuberculosis). There may also be crepitations at the bases, signs of pleural effusion and other signs as a result of congestive heart failure. Ulrich [302] also described palpable pulsation of the intercostal spaces due to systolic pulsation of the lungs as a result of the high pressure in the pulmonary vessels.

Cardiac Physical Signs.—Signs of cardiac disease to which the pulmonary vascular sclerosis is secondary may be present. Posselt [239] said that in cases of mitral stenosis with pulmonary vascular sclerosis the apical diastolic thrill tends to spread up the left sternal border and that sometimes there is a fine thrill at the pulmonary area which is increased by exertion and leaning forward. Dulness and tenderness are noted on percussion over the dilated pulmonary artery in the second and third spaces on the left side. There are a pulmonary systolic murmur transmitted to the left and an accentuated pulmonary second sound sometimes followed by a diastolic murmur, which is due not to functional incompetence of the pulmonary valve, as most persons think, but to the propagation upward of the mitral diastolic murmur. No one but Posselt has ever succeeded in eliciting these signs.

In the absence of mitral stenosis there are often no abnormal cardiac physical signs, though often the heart is enlarged to the right or to both the right and the left and the pulmonary second sound is accentuated. Occasionally there is a gallop rhythm on the right side, best heard near the lower end of the sternum.

Signs of Congestive Heart Failure.—Engorgement of the cervical veins, enlargement of the liver and edema were usually present before death in the cases that have been reported.

Polycythemia.—This is often present in cases of cyanosis, the highest recorded count being 9,430,000 erythrocytes, but it is not constant and there may be anemia.

Roentgenographic Observations.—The left middle arc of the shadow of the heart is formed by the pulmonary artery and the conus of the right ventricle. In the right anterior oblique view the middle of the three impressions on the barium-filled aorta is formed by the pulmonary artery.[225] The hilar shadows, according to Laubry,[159] are formed by the right and left pulmonary arteries. The pulmonary veins are normally invisible. In cases of hypertension of the pulmonary vessels the left middle arc is more prominent and longer and the hilar shadows are enlarged and pulsate more than normally, especially in cases in which there is incompetence of the pulmonary valves.[234] Ulrich [304] also described a "diaphragmatic dance," an up and down movement of the diaphragm that was synchronous with the heart beat. At this stage there may not be any symptoms, or there may be slight dyspnea and cyanosis on exertion. When heart failure occurs the hilar shadows become still wider and of uneven density and show indistinct edges. The lungs, especially centrally, are less transparent. This "syndrome of venous stasis" may be dissipated by treatment for heart failure, but the signs of the underlying pulmonary vascular hypertension persist. Sclerosis of the pulmonary artery rarely shows roentgenographically, as calcification is rare, but it is said that when there is marked sclerosis the pulsation of the left middle arc is diminished. Moniz [209] injected intra vitam from 6 to 8 cc. of a 120 per cent solution of sodium iodide directly into the right auricle by means of a long catheter introduced through a vein at the elbow. The pulmonary vessels were thus made radio-opaque and were visible in roentgenograms made directly after the injection. It is improbable that the information to be gained in this way can justify the risk to which the patient is exposed.

The electrocardiogram, in the few cases in which it was recorded, showed a preponderance of the right ventricle, sometimes with negative T waves in leads 2 and 3. Daly [68] showed in the dog that obstruction of the pulmonary artery causes the T wave in lead 3 to become more negative.

Course.—The course is usually said to be steadily downward, with progressive heart failure which is uninfluenced by treatment. However, many cases have been described in which temporary improvement occurred. Death is usually due to heart failure but occasionally to intercurrent infection. The duration of symptoms varies from a few months to forty-four years. Usually the patient dies within two years of the appearance of symptoms of heart failure.

ANALYSIS OF CASES

The cases in the present series have been analyzed to show the relationship of the secondary pulmonary vascular sclerosis to the clinical symptoms, as recorded in the case reports.

1. *Congestive Heart Failure.*—This was present in 25 of the 100 cases (fig. 17 and table 23). In 5 the right ventricle was normally thick, in 14 (56 per cent) moderately thick and in 6 (24 per cent) greatly thickened. Figure 17 shows that in all divisions of the pulmonary vascular bed the sclerosis was greater than it was in the 75 patients without heart failure, but it should be remembered that this group of 75 included a greater proportion of persons under 40. In each of the divisions of the pulmonary vascular bed greater sclerosis than in the cases of heart failure occurred in some one of the etiologic groups. Since greater sclerosis was often present without heart failure, it may be concluded that although the conditions causing heart failure also

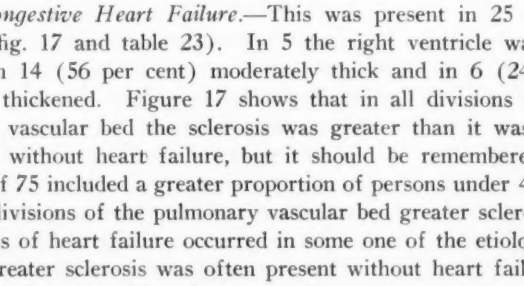

Fig. 19.—Graph showing the relationship of the degree of cyanosis to the degree of sclerosis found throughout the pulmonary vascular bed. The dot-and-dash line represents all the patients with cyanosis, the dotted line, all the patients without cyanosis.

favor the development of pulmonary vascular sclerosis, the sclerosis is not responsible for the symptoms of heart failure.

2. *Cyanosis* (table 27 and fig. 19).—Cyanosis was present in 17 cases. In 4 the right ventricle was normal, in 9 moderately thickened and in 4 greatly thickened. The average degree of sclerosis was greater than in the "no cause" group, but in each division of the pulmonary vascular bed the sclerosis was greater in some one of the etiologic groups. Moreover, the degree of sclerosis was only slightly less in the 83 patients without cyanosis. Thus, though cyanosis is often associated with marked pulmonary vascular sclerosis, the relationship cannot be direct since more marked sclerosis may occur without cyanosis.

3. *Polycythemia.*—The blood count was recorded in 47 cases. It was regarded as normal if it was between 4,500,000 and 5,000,000 and

TABLE 27.—*Relationship of Cyanosis to the Degree of Sclerosis Throughout the Pulmonary Vascular Bed*

	Sclerosis																											
	Stem of Pulmonary Artery		Large Elastic Arteries		Small Muscular Arteries		Arterioles and Venules		Small Veins		Large Veins		Extrapulmonary Pulmonary Veins		Muscularity of Veins			Thickness of Right Ventricle			Blood Count		
Patients with Cyanosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	Little	Moderate	Excessive	Normal	Moderately Thickened	Greatly Thickened	Low	Normal	High
17	11 65%	1.4+	16 94%	2.2+	17 100%	2.3+	15 88%	2.4+	15 88%	2.0+	11 65%	1.2+	6 8 lost 67%	1.4+	6 35%	2 12%	9 53%	4 24%	9 53%	4 29%	8 67%	3 25%	1 8%

TABLE 28.—*Relationship of the Blood Count to Sclerosis Throughout the Pulmonary Vascular Bed*

		Sclerosis																				
		Stem of Pulmonary Artery		Large Elastic Arteries		Small Muscular Arteries		Arterioles and Venules		Small Veins		Large Veins		Extrapulmonary Pulmonary Veins		Muscularity of Large Veins			Thickness of Right Ventricle			
Blood Count	No. of Patients	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	Little	Moderate	Excessive	Normal	Moderately Thickened	Greatly Thickened	Cyanosis
Low (under 4.5×10^6)	27	13 1 lost 50%	0.8+	26 96%	1.8+	25 92%	2.1+	25 92%	2.3+	25 92%	2.3+	17 63%	1.4+	9 16 lost 82%	1.5+	14 52%	6 22%	7 26%	13 48%	10 37%	4 15%	8 30%
Normal (4.5 to 5.5×10^6)	13	8 1 lost 67%	1.1+	13 100%	1.8+	11 85%	1.9+	12 92%	2.2+	12 92%	1.8+	5 1 lost 33%	0.6+	4 8 lost 80%	1.8+	7 58%	2 17%	3 25%	8 67%	3 25%	1 8%	3 23%
High (over 5.5×10^6)	7	4 57%	1.3+	6 1 lost 100%	2.2+	7 100%	1.4+	7 100%	2.7+	7 100%	2.0+	2 3 lost 50%	0.5+	1 6 lost	1.0+	2 90%	2 90%	1 20%	3 43%	4 57%	0	1 14%

low and high if below or above these limits, respectively. Table 28 and figure 20 show that no relationship could be traced between the blood count, the thickness of the right ventricle and the presence of cyanosis or sclerosis of the pulmonary vessels.

4. *Hypercyanotic Angina.*—This occurred only in the boy with primary pulmonary vascular sclerosis and will be discussed under that heading.

5. *Hemoptysis* (table 29).—This occurred in 9 cases, in 5 of which the right ventricle was thickened. The average degree of sclerosis was somewhat greater in all divisions of the pulmonary vascular bed than in the "no cause" group but was less in each division of the pulmonary vascular bed than in some of the etiologic groups. Thus, though the factors which cause hemoptysis also favor the development of pulmo-

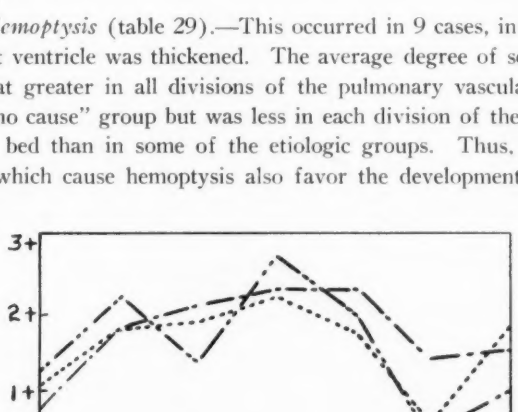

Fig. 20.—Graph showing the relationship of the blood count to the degree of sclerosis found throughout the pulmonary vascular bed. The dot-and-dash line represents patients with a low blood count; the dotted line, the patients with a normal blood count, and the two-dots-and-dash line, the patients with a high blood count.

nary vascular sclerosis, there is no reason to believe that there is any direct relationship between the two.

6. *Electrocardiography.*—In 12 cases (table 30) electrocardiograms were made. In the 3 patients with normal electrocardiograms there was fairly marked sclerosis, though less than in those with abnormal electrocardiograms. It is interesting to note that the right ventricle was greatly thickened in all 4 patients with left axis deviation, in 1 of the 3 with normal tracings and in 1 of the 4 with intraventricular block (in the remaining 3 of these it was moderately thickened). The electrocardiogram, therefore, gives no information as to the state of the pulmonary vascular bed.

TABLE 29.—*Relation of Hemoptysis to the Degree of Sclerosis Throughout the Pulmonary Vascular Bed*

TABLE 29.—*Relation of Hemoptysis to the Degree of Sclerosis Throughout the Pulmonary Vascular Bed*

		Sclerosis																					
		Stem of Pulmonary Artery		Large Arteries		Small Muscular Arteries		Arterioles and Venules		Small Veins		Large Veins		Extrapulmonary Veins		Muscularity of Large Veins			Thickness of Right Ventricle				
No. of Patients		No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	Little	Moderate	Excessive	Normal	Moderate	Excessive	Cyanosis
9		7 1 lost 88%	1.5+	9 100%	1.9+	9 100%	2.1+	9 100%	2.2+	8 89%	2.3+	5 1 lost 63%	1.4+	3 5 lost 75%	1.8+	4 50%	1 13%	3 37%	4 44%	3 33%	2 22%	3 33%

TABLE 30.—*Relation of the Electrocardiographic Observations to the Degree of Sclerosis Throughout the Pulmonary Vascular Bed*

		Sclerosis																					
		Stem of Pulmonary Artery		Large Arteries		Small Arteries		Arterioles and Venules		Small Veins		Large Veins		Extrapulmonary Pulmonary Veins		Muscularity of Large Veins			Thickness of Right Ventricle				
Electrocardiographic Observation	No. of Patients	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	Little	Moderate	Excessive	Normal	Moderate	Excessive	Cyanosis
Normal	3	2	0.7+	3	1.7+	3	2.0+	3	1.7+	3	2.3+	2 1 lost	2.0+	2 1 lost	2.0+	0	1	2	1	1	1	1
Right axis deviation	1	1		1		1		0		0		0		0		..	1	..	..	..	1	1
Left axis deviation	4	1	2.0+	4	2.8+	4	2.0+	4	2.8+	4	2.8+	2 1 lost	1.0+	..		0	2	1	0	0	4	1
Intraventricular block	4	3	1.3+	3	2.3+	4	2.5+	4	2.8+	4	2.8+	3	1.5+	1 3 lost		0	2	2	0	3	1	2

SUMMARY

Thus, sclerosis in the vessels of the pulmonary circulation is almost constantly found at autopsy, though often it is only slight. It is as common as systemic vascular sclerosis, though usually not so severe. This robs pulmonary vascular sclerosis of much of the significance that has been attached to it. Like systemic vascular sclerosis it may exist without producing any obvious harmful results. Indeed, it is much less dangerous than systemic arteriosclerosis, since it is much more difficult to cause infarction of the lungs by occluding its vessels than in organs such as the heart or brain. If infarcts are produced, the rest of the lung is easily able to take over the function of the portions destroyed, so that disastrous consequences, such as those of infarction of the brain or heart, are not produced. Harmful results of pulmonary vascular sclerosis may be expected to follow only if the sclerosis so obstructs the pulmonary circulation as to embarrass the right ventricle. It is known that the most extreme systemic vascular sclerosis may occur without a rise in the systemic blood pressure or any embarrassment of the left ventricle, though with great aortic atheroma, owing to loss of elasticity of the aorta, the systolic pressure may be slightly raised and the diastolic pressure slightly lowered. It has been suggested that this may also occur in cases of sclerosis of the large pulmonary arteries, but if it does, it is not likely to embarrass the right ventricle seriously.

The present investigation shows that in the majority of cases of even severe pulmonary vascular sclerosis there are no circulatory symptoms, and that in 24 of the 25 patients with circulatory symptoms there was present some disease of the heart or lungs which could adequately account for the circulatory symptoms, even in the absence of pulmonary vascular sclerosis. The exception was an example of the unusual condition of primary sclerosis and will be discussed in the next section. It may therefore be concluded that pulmonary vascular sclerosis is common but only rarely of clinical importance.

(To be concluded)

PULMONARY ABSCESS AND PULMONARY GANGRENE

ANALYSIS OF NINETY CASES OBSERVED IN TEN YEARS

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AND
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In the past ten years at Mount Sinai Hospital (two hundred and seventy beds), fifty-five cases of pulmonary spirochetosis, better designated Miller-Vincent's infection of the lung, including thirty-nine cases of pulmonary gangrene, have been observed, as well as twelve cases of bronchogenic pulmonary abscess and twenty-three cases of embolic pulmonary abscesses.

The embolic pulmonary abscesses were associated with areas of suppuration elsewhere in the body and were manifestations of generalized pyemia or bacteremia.

Of the local bronchogenic pulmonary lesions, gangrene was observed more than three times as frequently as abscess. Although all the cases presented clinically the picture of so-called typical abscess of the lung, they were usually readily recognized by distinguishing characteristics as cases of gangrene and abscess, respectively. Of the thirty-nine cases of gangrene, thirty-two were in adults and seven in children. Of the twelve cases of bronchogenic abscess eight were in children and four in adults. Twenty-two cases of pulmonary gangrene followed an operation, which in all but a few instances was performed under general anesthesia. Half the operations were on the oral cavity. This incidence emphasizes the danger of aspiration of infective material from the oral cavity, especially during general anesthesia.

Ninety-six per cent of the patients with embolic pulmonary abscess died. The mortality in cases of bronchogenic abscess was 58 per cent. In contrast to these results are those in the cases of properly treated patients with pulmonary gangrene with cavitation, a much more severe process than pyogenic abscess. In twenty-five such cases, mortality was only 32 per cent. Mortality in the whole group of cases of gangrene, including fourteen in which there was no treatment with arsenic

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or only one treatment when the patient was practically moribund (within four days of death), was 49 per cent.

Although at times it is a problem clinically and anatomically to distinguish abscess, putrid abscess and early gangrene with the organisms both of suppuration and of gangrene present, this difficulty does not justify the consideration of pulmonary gangrene and abscess of the lung as one entity. Pyogenic organisms never produce gangrene, whereas the fully developed and characteristic lesion produced by spirochetes, fusiform bacilli and vibrios is not abscess, but gangrene.

The sputum in the cases of pulmonary gangrene was foul-smelling, grayish brown or grayish green and occasionally blood-streaked or bloody, and, when washed free of oral mucus, it was found to contain characteristic oral spirochetes, fusiform bacilli and vibrios (the Miller-Vincent organisms).[1] In the cases of abscess, on the other hand, the sputum was whitish yellow, mucopurulent or purulent, without appreciable odor, and contained pyogenic organisms, usually staphylococci.

In the cases of bronchogenic abscess, at autopsy the lesion was usually found limited to one lobe (to a lower lobe most frequently), was not infrequently multiple and was at times confluent and associated with a regional pneumonia, but not with pyemia or bacteremia. The abscesses varied in size, were reddish gray or grayish yellow and did not have an appreciable odor. In a few cases in the early stage, the lesions were reddish. Smears and cultures showed staphylococci in all the cases. Sections of early lesions stained by the Gram method showed numerous clusters of staphylococci in the bronchial branches and in the alveoli, whereas the regional blood vessels were not involved.

In the cases of gangrene, on the other hand, the fully developed characteristic lesion was ragged, penetratingly foul-smelling, and brownish or greenish, and smears and sections from it showed innumerable spirochetes, fusiform bacilli and vibrios (Miller-Vincent's organisms). As in bronchogenic abscess, gangrene was limited usually to one lobe, most frequently to a lower lobe. At times, however, more than one lobe was involved in the process.

As not more than several hundred cases of pulmonary spirochetosis have thus far been reported in the United States (one hundred and eighteen cases collected by Smith up to November 1927 [2]), it is probable that many cases diagnosed as instances of pulmonary abscess from clinical and roentgenologic evidence, but not supplemented by a study

1. Kline, B. S., and Berger, S. S.: The Relation of Oral Spirochetosis to Pulmonary Gangrene, J. Am. Dent. A. **15**:64, 1928.

2. Smith, D. T.: Fuso-Spirochaetal Disease of the Lungs: Its Bacteriology, Pathology and Experimental Reproduction, Am. Rev. Tuberc. **16**:584, 1927; Oral Spirochetes and Related Organisms in Fuso-Spirochetal Disease, Baltimore, Williams & Wilkins Company, 1932.

of the sputum as we have outlined, were, in reality, cases of pulmonary gangrene.

In addition to the thirty-nine cases of fully developed pulmonary gangrene with sputum containing the Miller-Vincent organisms, there were six cases of pneumonitis and eight cases in which the involvement was limited to the bronchi, some patients having associated bronchiectasis, in which the sputum contained these organisms. In the majority of the cases of pulmonary gangrene observed clinically, the pleura was involved, frequently so severely as to require thoracostomy; in two cases, following repeated thoracentesis, gangrenous cellulitis of the wall of the chest developed (thoracentesis in these cases is now considered contraindicated unless it is to be followed promptly by resection of the ribs and pleural drainage in the traumatized area). Among the cases of Miller-Vincent's infection were two in which the lesion was apparently limited to the pleura. One case of this series was associated with active pulmonary tuberculosis.

Arsphenamine therapy was particularly efficacious in the cases of pneumonitis with sputum containing Miller-Vincent's organisms. The most striking results, however, were obtained in the cases of frank gangrene. Seventeen of twenty-five seriously ill patients who were intensively treated with arsphenamine recovered. Large or maximum doses were given every two or three days as a routine, except in some of the earlier cases.[3] The favorable results in gangrene are in marked contrast to only five recoveries in twelve cases of bronchogenic abscess, a less severe process.

In addition to arsenical therapy the patients with Miller-Vincent's infection received treatments indicated by the symptoms and general condition. Toxemia, general debilitation, insomnia, excessive cough, hemorrhage and anemia were combated with the usual therapeutic measures. In general, transfusions, a diet high in calories, inhalations of oxygen and supportive measures of all kinds were employed. Postural drainage was used as a routine, as in the treatment of abscess, and should never be neglected. Bronchoscopic drainage was found useful in the early stages of cavitation.

In several cases of pulmonary gangrene phrenicectomy or phrenicotomy was done on the involved side. Artificial pneumothorax may be employed; the indications are the same as for lesions other than Miller-Vincent's infection. The lesion must be far enough from the periphery of the lung that rupture and empyema will not occur. It is well to bear in mind that by compression of the lung anaerobic conditions are favored and that a flare-up of the infection may follow. Likewise,

3. Kline, B. S., and Berger, S. S.: Spirochetal Pulmonary Gangrene Treated with Arsphenamins, J. A. M. A. **85**:1452 (Nov. 7) 1925.

drainage from the compressed area may be hindered. Phrenicectomy may be employed for basal lesions, but the contraindications are the same as for artificial pneumothorax. These measures are more suitable for the treatment of abscess than for that of gangrene. When phrenicectomy or artificial pneumothorax is employed chiefly, arsenic therapy should be continued. The open operation is preferable whenever it can be safely employed.

Wassermann tests and slide precipitation tests for syphilis in cases of pulmonary spirochetosis (Miller-Vincent's pneumonitis, gangrene, bronchitis, pleuritis) gave positive results only in cases of syphilis in addition to the nonsyphilitic pulmonary lesion. A few uncomplicated cases gave doubtful results in the Wassermann or slide tests.

The spirochetes, fusiform bacilli and vibrios (Miller-Vincent's organisms) of pulmonary gangrene are identical with those present in

TABLE 1.—*Incidence of Postoperative Pulmonary Complication in Persons Treated and Not Treated*

	Service Patients Treated				Private Patients Not Treated			
	Surgical Operations	Pulmonary Complications	Percentage	Fatalities	Surgical Operations	Pulmonary Complications	Percentage	Fatalities
1928.....	1,024	1	0.097	0	2,261	16	0.7	4
1929.....	1,294	4	0.31	1	2,520	14	0.55	4
1930.....	1,296	2	0.15	1	1,945	19	0.97	8
1931.....	1,464	2	0.13	0	2,171	11	0.5	2
Total.....	5,078	9		2	8,897	60		18
Average.....			0.17				0.68	

the mouth in practically all adults (in the interproximal spaces between the gums and teeth). The lesion perhaps most frequently produced by these organisms is gingivitis. When observed early, the gums are somewhat swollen and injected and bleed readily on pressure. The commonest sites are adjacent to the rear molars. Overlying the swollen gums is usually a yellowish-white exudate which contains the characteristic spirochetes, fusiform bacilli and vibrios in large number. This lesion, although frequently overlooked by the patient and by the physician, is a menace to health, since from it the organisms may be aspirated into the lung and so produce gangrene.

For the past six years, under the direction of Dr. M. B. Galvin, the dental service of Mount Sinai Hospital has given preoperative oral therapy to patients in the public wards. Table 1 shows the incidence of postoperative pulmonary complication in persons treated and in those not treated from 1928 to 1931 inclusive. The results give evidence that pulmonary infections, including those by the Miller-Vincent organisms, may be prevented by proper oral hygienic or therapeutic measures.

CLINICAL OBSERVATIONS AND PATHOLOGY

PULMONARY ABSCESS

Embolic Pulmonary Abscess.—In the series reported here there were twenty-three cases of staphylococcic bacteremia or pyemia with embolic pulmonary abscesses. Of these, fourteen were in infants or children, and nine were in adults. One patient recovered, and twenty-two died. In sixteen cases a postmortem examination was made.

The embolic abscesses involved a number of lobes, were multiple and relatively small and were associated with areas of suppuration elsewhere in the body, representing a manifestation of pyemia or bacteremia. The clinical evidences of pulmonary involvement in the acute cases were not particularly striking and were masked by the symptoms of general sepsis. The high mortality and the high incidence of the condition in infants and children are noteworthy.

The embolic abscesses observed at autopsy in this series were multiple, usually small (from 5 to 15 mm. in diameter) and more or less spherical, occurring in a number of lobes and associated with areas of suppuration elsewhere in the body (in the kidneys, in the myocardium and occasionally in the brain). The lesions were grayish or yellowish and soft or viscid, with little or no odor. In a few cases in which the lesions were numerous, they were coalescent in places. Early lesions were reddish and more coherent. In some cases there were infarction and suppuration, with the lesions more or less wedge-shaped, larger than embolic abscesses and situated along the lower borders of the lobes. A number reached and involved the pleura. Smears and cultures showed the pyogenic organisms. In sections stained by the Gram method, abundant organisms were observed in and about occluded blood vessels. The involved pulmonary tissues were necrotic and usually completely replaced by pus.

Bronchogenic Pulmonary Abscess.—In the second group in this series, that of bronchogenic pulmonary abscess, there were twelve cases. Ten patients were male and two were female; there were eight infants and children and four adults. There was complicating bronchitis or pneumonia in eight cases. The condition developed following operation under general anesthesia in three cases and following operation under local anesthesia in one. The location of the lesions is indicated in table 2.

This type of abscess is aspiratory and, like embolic abscess, occurs most frequently in infants and children. It is usually limited to one lobe, a lower lobe most frequently. There may be multiple abscesses, however, and these at times are confluent. The abscess or abscesses are associated with regional pneumonia. A bronchogenic abscess is not associated with pyemia or bacteremia. In eight of the twelve cases in

the series there was no relation to a surgical procedure. The abscesses varied in size; the sputum did not have an appreciable odor, and the smears and cultures showed staphylococci in all cases. In one patient it was associated with an infection caused by Bacillus pyocyaneus. Five of the twelve patients recovered. The symptoms are those of pneumonia, which the abscess complicates; however, resolution fails to take place. In its stead, when the abscess begins to break down, abundant purulent material, at times blood-streaked, is expectorated. The odor, when present, is not distinctive and is never foul as in gangrene. Evidence of clubbing of the fingers may be present, appearing at times with surprising rapidity.

Signs of a cavity can be elicited both by physical and by roentgen examination as early as eight or ten days after the onset of symptoms. The spontaneous evacuation of the abscess through the bronchus may take place promptly and healing begin. This occurred in five of the twelve cases. When the lesion is progressive and a large area of suppuration appears the symptoms of toxemia with high fever, leukocytosis and progressive exhaustion develop, and death frequently results. This occurred in seven of twelve cases (mortality, 58.3 per cent) in spite of supportive measures, including postural and bronchoscopic drainage. It should be noted that the greater incidence of bronchogenic abscess in children probably depends on the fact that the oral flora at this time contains more staphylococci than later in life and that before 10 years of age children ordinarily do not harbor in their mouths appreciable numbers of spirochetes, fusiform bacilli and vibrios.

In contrast to the postmortem picture in embolic abscesses, the suppuration in cases of bronchogenic abscess was found limited to the lung only. Multiple lesions were occasionally found, but the process was usually limited to one or a few foci in one lobe. The lower lobes were most frequently involved. The lesions in general were larger than embolic abscesses and associated with areas of bronchopneumonia.

The local lesion was usually several centimeters or more in size, irregular in shape, at times owing to the coalescence of foci, and surrounded by inflamed lung tissue. The involved area was soft or viscid, gray, yellow or yellow-brown, with little or no odor unless the organisms of gangrene were present. Early lesions were reddish and hardly distinguishable from areas of pneumonia. Smears and cultures showed the pyogenic organisms, usually staphylococci, together with other oral cocci. In one case colon bacilli were present. In another B. pyocyaneus was also present.

Sections of early lesions stained by the Gram method showed numerous clusters of staphylococci in the bronchial branches and alveoli.

whereas the regional blood vessels were uninvolved. A case with characteristic findings is reported:

S. L., aged 6 months, was admitted to the hospital with signs of an incarcerated inguinal hernia on the right side. The patient was acutely ill, with a temperature of 102 F. She was operated on under local anesthesia. On the following day, the temperature rose to 105.5 F., the pulse rate ranged between 160 and 200 and the respiratory rate was between 60 and 80. Fine crepitant râles and dulness were present over the base of the chest on the left, and high-pitched distant tubular breath sounds were heard. There was marked abdominal distention. Three days after the operation the patient died. Autopsy revealed bronchopneumonia with a small abscess in the upper lobe of the left lung, fibrinopurulent pleurisy and local peritonitis.

PULMONARY SPIROCHETOSIS

The invasion of the pulmonary tissues by Miller-Vincent's organisms may induce bronchitis, pneumonitis, gangrene, pleurisy or a combination of these. The organisms concerned are generally present in the mouth of persons over 10 years of age, between the gums and the teeth and occasionally in the sinuses and the nasopharynx. Not infrequently, when local conditions permit, they multiply enormously and cause from mild to severe inflammation and gangrenous ulceration. Patients and physicians are frequently unaware of mild lesions which may be teeming with these organisms, free on the surface in the upper respiratory tract. Gingivitis containing these organisms about the rear molars is especially common.

The penetration of the lungs by organisms is favored when the cough reflex is abolished, as when the patient is under a general anesthetic or during deep sleep. Occasionally, infected food or other particles are accidentally aspirated into the trachea during full consciousness and cannot be coughed out.

Between the time of aspiration of the infected material and the onset of symptoms several days usually elapse. However, symptoms may be apparent within two days or may not appear until fourteen days later. The relationship between aspiration and the onset of symptoms may be definitely timed in those cases which occur following operation under general anesthesia. The infected material is aspirated into the lung during the period of anesthesia, and the resulting lesions depend on the amount of aspirated material, the number and virulence of the invading organisms and the local and general resistance of the patient. Symptoms and physical signs resulting from invasion of the pulmonary tract may appear within forty-eight hours or even earlier.

In those instances in which symptoms first appear several weeks after operation, it is probable that the aspiration of the infected material occurred within fourteen days prior to the onset of symptoms and is without any relation to the operation, as in those cases in which the

condition arises apparently spontaneously when no operation under general anesthesia has been performed. The symptoms in cases of Miller-Vincent's infection of the lungs also vary depending on whether the infection is primary or whether it is superimposed on some other condition.

The fifty-five cases of Miller-Vincent's infection of the lung were distributed as follows:

Type	No. of Cases
Gangrene	39
Pneumonitis	6
Bronchitis	8
Pleurisy	2

The age incidence was:

Age, Years	No. of Cases
3 to 9	4
10 to 19	3
20 to 29	12
30 to 39	11
40 to 49	12
50 to 59	6
60 to 69	7
	55

It is noteworthy that the greatest number of cases (thirty-five of fifty-five, or 64 per cent) occurred in the age groups between 20 and 50 years. In contrast to abscess, which occurred twice as often in children as in adults, Miller-Vincent's infection of the lung occurred seven times as often in adults as in children (forty-eight adults, seven children).

In the majority of cases, there was moderate leukocytosis. The average white blood cell count in the fifty-five cases was 16,000. In one case (table 3, case 22) in which the disease progressed rapidly and resulted in death eleven days following the onset, there was granulocytopenia with the following white cell count:

Date	White Blood Cell Count
5/28	20,000
5/31	13,000
6/2	10,000
6/3	1,650
6/4	1,250
6/5	750
6/6	800
6/7	420
6/8	400
6/9	330
6/12	270

This fulminating case of acute gangrene of the lungs followed the extraction of a tooth and alveolectomy for gangrenous osteomyelitis under general anesthesia.

Anemia of the secondary type was observed in many cases and usually was not severe. Transfusion as a supportive measure was used with benefit.

In the acute Miller-Vincent's infection of the respiratory tract, fever is always present. In the parenchymatous pulmonary type the temperature may reach 105 F. In the chronic state, fever may be absent except during periods when the gangrenous purulent material is retained.

Cough is always present, with the same characteristics as are found in acute and chronic bronchitis, bronchiectasis and cavitation. The general symptoms depend on the stage of the involvement. In the acute stage the clinical process is indistinguishable from bronchitis, pneumonia or abscess. In the subacute stage it may resemble tuberculosis, bronchiectasis or abscess, and in the chronic stage the symptoms are those of a chronic suppurative disease of the lungs with the formation of cavities. The fetid character of the breath and of the foul sputum in all these conditions practically makes the diagnosis, and the presence of Miller-Vincent's organisms in the washed sputum establishes it.

Pulmonary Gangrene.—There were thirty-nine cases of pulmonary gangrene in this series (over three times the number of cases of bronchogenic abscess observed), thirty-two in adults and seven in children, twenty-five in males and fourteen in females. The youngest patient was 3 years of age, and the oldest, 69. Seventeen cases followed operation (eight oral, nine nonoral) under general anesthesia, four followed operation (two oral, two nonoral) under local anesthesia and seventeen had no relation to operation.

Pulmonary invasion in these cases was usually ushered in with fever and occasionally with chills, pain in the chest and cough and expectoration, symptoms which usually led to the diagnosis of pneumonia. At first, the physical signs and roentgen observations could not be differentiated from those of ordinary pneumonitis. The history and the character of the sputum, however, made possible the prompt diagnosis of Miller-Vincent's infection. The sputum, which at first may be mucopurulent and occasionally hemorrhagic and without appreciable odor, soon becomes abundant, thin, gray or brown-green, with an intensely foul odor, and microscopic examination reveals the characteristic oral spirochetes, fusiform bacilli and vibrios (Miller-Vincent's organisms).

Pulmonary gangrene and pulmonary abscess should not be confused with each other, for they are two distinct and well defined diseases.

Failure to recognize this may result in unnecessary loss of life, since pulmonary gangrene with characteristic etiology and pathology may be combated by specific therapy which is much more efficacious than are the measures for pulmonary abscess.

The process in the lung in gangrene is one of progressive ulceration in the pneumonic areas, resulting in the formation of cavities of which there may be one or more scattered throughout one or more lobes. The cavities vary in size and differ from tuberculous cavities in that they are free from trabeculations. In the former the process is more fulminating, and the destruction is complete. In this stage both the physical signs and roentgenograms readily reveal the presence of cavities. The characteristic fluid level or the fluid and air, which shift with a change in position, may readily be demonstrated. In some cases early detection depends on both physical and roentgen examination, especially following postural drainage.

In the early stages, before the communication with the bronchus is fully established, there may be only one evacuation of foul-smelling sputum from the area of cavitation containing the organisms, blood and necrotic lung tissue, and a number of days may elapse before communication is again established and similar sputum is brought up. The patient is always aware of having expectorated this foul-smelling material and when questioned invariably reveals it. If the communication between the cavity and the bronchus is intermittent, the sputum brought up at times fails to have the characteristic odor and is devoid of the characteristic Miller-Vincent organisms, in which case an early diagnosis is missed.

The expectoration of foul-smelling sputum in the presence of an unclean mouth, a history of a recent operation or a preexisting pulmonary condition, such as pneumonia, tuberculosis or a neoplasm, on which gangrene may be superimposed makes the diagnosis of pulmonary gangrene probable. In the more advanced stages of gangrene, the odor is so pronounced that entrance into the room is sufficient for a probable diagnosis, since both the sputum and the breath are sickeningly foul, and the odor completely permeates the room. Examination of the washed sputum and physical and roentgen examination readily reveal conclusive evidence of the Miller-Vincent infection.

In a few cases in the series the signs, symptoms and anatomic observations were those of pulmonary gangrene without appreciable pneumonitis or a preexisting pulmonary lesion. These were of a fulminating type, with a rapid course, speedily terminated by death. In the majority of the cases, however, the findings were those of gangrene and cavitation following pneumonitis. The course was a matter of weeks or months, reflecting a less severe process, and to the signs and symptoms of pneumonitis those of cavitation were promptly added.

Early in the fulminating, and later in the less severe, types, pneumonitis may be followed by complete resolution, but not infrequently the process becomes arrested only to become active again if treatment is discontinued. In some cases the process is slowly progressive. In the subacute and chronic types the development is more insidious and the systemic reaction less marked. The subacute and chronic types either result from primary spirochetosis or represent a secondary superimposed invasion on a previous lesion in the lung, such as old chronic bronchitis, bronchiectasis, tuberculosis or tumor of the lung. Subacute and chronic types may flare up into an acute process with gangrenous destruction of the tissues and assume all the aspects of the more acute, menacing lesion.

In one case the gangrenous process complicated active tuberculosis of the lungs. There was no apparent benefit following arsphenamine therapy, and the tuberculous process steadily progressed, causing death after several months.

It is of the utmost importance to make the diagnosis of pulmonary infection with the Miller-Vincent organisms as soon as possible, in order to prevent the extensive gangrenous ulcerative processes which these organisms produce. Antisyphilitic therapy with arsphenamine is most effective when begun early. Arsenic in the form of arsphenamine or neoarsphenamine, administered to the point of causing toxicity, is the most valuable single measure in the treatment of pulmonary gangrene.

In the acute stage, intensive treatment is necessary to prevent rapid gangrenous destruction. The arsphenamine should be administered intravenously in appropriate dosage, according to the age and weight of the patient, and should be given in full doses every other day or every third day until improvement is manifest. The temperature, pulse, toxemia and character of the sputum (diminution of the odor) are the guides. Later treatment should be administered every four days, with the physician alert for the onset of symptoms of arsenic poisoning, i. e., itching of the skin, gastro-intestinal upset, renal damage and jaundice. Treatment should be continued until all the symptoms of the infection have disappeared, the sputum has lost its odor and the physical signs have disappeared. Beside the physical signs, roentgen examination is helpful in depicting the course of the disease. It has been our experience that acute bronchitis, acute pneumonitis and even early gangrene with cavitation heal when energetic treatment is given. In most instances, arrest of the activity of the Miller-Vincent organisms can be accomplished if energetic treatment is begun promptly within one to two weeks after the onset of symptoms. When the spirochetal invasion is secondary, specific therapy will arrest only the process due to it, and the associated condition, such as tuberculosis, tumor or some other chronic pulmonary condition, may go on indefinitely.

In the acute stage, in addition to arsphenamine therapy, oxygen administered under pressure in a tent is advisable. It is needless to stress the fact that supportive measures of all kinds, hydrotherapy (especially when the temperature is high and toxemia is great) and control of excessive cough, assuring rest and sleep, are always indicated. In the subacute stage, as soon as the patient is able, postural drainage should be carried out. Bronchoscopic drainage in this stage is at times followed by prompt healing. If, in spite of these measures, cough, abundant sputum with odor, continued impairment of the general health and clubbing of the fingers develop, the more chronic stage with cavitation is established. If the acute gangrenous process results in the formation of cavities, and healing under intensive treatment has not taken place at the end of from four to six weeks, healing of the cavitation is unlikely to occur therafter, and the chronic stage with the usual sequelae of the formation of cavities is established. This condition must be dealt with according to the general condition of the patient and the location and number of the cavities. When arsphenamine and postural and bronchoscopic drainage, with general supportive measures, fail to accomplish healing in from four to eight weeks after the onset, pneumothorax or phrenicectomy may be tried. The use of iodized poppy-seed oil 40 per cent is helpful in determining the location and the extent of the lesions and in indicating further therapy.

If no pleural adhesions are present, if the cavity is limited to one lobe and is not too near the periphery but near the hilus, artificial pneumothorax may be tried. Phrenicectomy may be tried when the lesion is not too near the periphery but is in the lower lobe near the diaphragm. When the condition does not yield to these measures, when the cavity is large or when there are several which may be intercommunicating, surrounded by a dense wall and infiltration, the more formidable surgical procedure of external drainage is necessary for the eradication of infection. This is the operation of choice. The cautery operation of Graham (which can be done in several stages to diminish the shock of a more extensive one-stage operation) may be successful in the hands of experienced surgeons. Lobectomy also has been successfully performed by some. These procedures, however, are more dangerous.

At autopsy, in contrast to the grayish or yellowish suppuration with little or no odor in cases of abscess, the lesions in cases of pulmonary gangrene were ragged, brownish or greenish and penetratingly foul-smelling.

Pulmonary gangrene, like bronchogenic abscess, was found most frequently in the lower lobes. Occasionally more than one lobe was found to be involved. In the majority of cases gangrene was found involving pneumonic areas. In the acute cases, however, in which countless oral

anaerobes had been aspirated into the lungs from lesions in the upper respiratory tract, there was little regional pneumonia.

Sections stained with hematoxylin and eosin, by the Levaditi method and, best of all, by the Warthin and Starry methods, showed that the gangrenous process begins in and about the smaller bronchial branches with the first characteristics those of bronchopneumonia, followed by necrosis of the exudate and of the fixed tissue. Following this, the lesion steadily enlarges, and ulceration occurs in the older areas of necrosis. The lesion now is fully developed and characteristic of gangrene, consisting of a ragged, penetratingly foul-smelling, brownish or greenish ulcerated area, with innumerable oral spirochetes, fusiform bacilli and vibrios present not only in the areas of necrosis, but also at the advancing periphery. In a short time there is coalescence of the ulcers, with the formation of definite cavities and since no tissues are spared in the progression of the gangrenous lesion, no large ridges or bridges of tissue ordinarily remain. In the cases with ulceration or frank cavity formation the contained material consists not only of necrotic lung tissue and exudate but of innumerable bacteria, including the Miller-Vincent organisms and ordinary aerobic oral bacteria.

In some cases gangrenous cavities showed evidence of partial healing, with granulation tissue in the wall. In one case in another series several healed cavities with intact epithelial lining were present, together with more recent gangrenous cavities, extensive pneumonitis and a terminal large area of gangrene of the brain, all active lesions containing the characteristic Miller-Vincent organisms.

In the cases of gangrene and in those of abscess of the lung the pleura was frequently involved, and not uncommonly there was gangrenous effusion or empyema.

Gangrene was found complicating active pulmonary tuberculosis in one case in this series and has been reported involving degenerating tumors of the lung.[4]

The following report is of a characteristic case:

N. M., a woman, aged 33, had a tonsillectomy under general anesthesia on Sept. 2, 1924. She apparently was making a good recovery until September 13, when she complained of pain in the right side and had a high temperature and cough. Seen on September 15 in consultation, she showed well marked signs of infiltration of the upper lobe of the right lung. The temperature was 104 F., and there was marked prostration. The odor of the sputum was intensely foul, and it greatly annoyed the patient. A diagnosis of gangrene of the lung was made. The washed sputum showed innumerable Miller-Vincent organisms. The roentgen examination, made on September 18, revealed marked density in the upper part of the chest on the right side, with a cavity about the size of a silver dollar in the infraclavicular area. Treatment with sulpharsphenamine was instituted. The patient

4. Seecof, David: Personal communication to the authors.

made an uneventful recovery, and at the end of four weeks was able to leave her bed. Seven months later roentgen examination failed to reveal any evidence of the cavity.

This report illustrates a case of pulmonary gangrene with the formation of a cavity with complete healing following arsphenamine therapy. The diagnosis was made promptly, and energetic treatment was instituted, to which the complete healing may be attributed.

Pneumonitis with the Miller-Vincent Organisms.—There were six cases in the series, four in men, and two in women: one following operation (nonoral) under general anesthesia, one following oral operation with no anesthetic, and four having no relation to surgical procedure. All the patients recovered quickly following specific therapy.

The signs and symptoms in these cases were essentially those of ordinary pneumonitis of one or two lobes. In some the picture suggested postinfluenzal pneumonia, and in some lobar pneumonia was the first impression. In one case the picture suggested pulmonary tuberculosis.

As shown in table 2, none of the patients with pneumonitis or bronchitis caused by Miller-Vincent's organisms died. One of the two patients in whom the lesion was limited to the pleura died, but postmortem examination was not permitted. In a number of cases of pulmonary gangrene, however, autopsy showed areas of pneumonitis containing the Miller-Vincent organisms, and in all of the cases there was bronchial involvement of varying degree. Furthermore, in many of the cases there was involvement of the pleura, and not infrequently gangrenous effusion was present.

In the areas of pneumonitis in the cases of gangrene the picture was not unlike that of ordinary bronchopneumonia with some interstitial involvement. In portions of the involved lung in some cases the lesion was that of bronchopneumonia with degenerative and necrotic changes of the cells of the exudate and fixed tissue. This lesion resembles somewhat the necrotizing lesion in certain stages of exudative tuberculosis. Smears and sections from areas of intact and necrotizing pneumonitis showed the characteristic Miller-Vincent organisms, together with a variable number of ordinary aerobic oral bacteria. In portions of the pneumonic areas in some cases, organization of the exudate was observed. As stated earlier, six patients in the series showed lesions apparently of this nature, without definite ulceration detectable by clinical or roentgen examination.

Miller-Vincent's Infection of the Bronchi.—There were eight cases: seven in men and one in a woman. The symptoms were much like those in cases of bronchitis caused by other organisms, and they depended on whether the condition was acute or chronic or an exacer-

bation of a chronic infection. A few cases showed signs and symptoms of bronchiectasis. The distinguishing character of the infection was made clear by the sputum. This was markedly fetid and contained the characteristic Miller-Vincent organisms. In these cases pulmonary hemorrhages occurred frequently, and the condition could readily be mistaken for pulmonary tuberculosis, neoplasm or the like. The general well-being of the patient with little systemic reaction, however, helps in the differentiation. In one instance, there was polycythaemia vera with enlargement of the spleen.

Chronic bronchial and chronic parenchymatous infections with the Miller-Vincent organisms, including bronchopulmonary cavity, may be present for years. This infection may dominate the picture or it may be found merely in association with other bronchopulmonary conditions. These processes may exist for years and be considered chronic bronchitis, bronchiectasis or tuberculosis, and usually the Miller-Vincent infection is unrecognized until an acute exacerbation with gangrene or some intercurrent infection or complication such as a gangrenous lesion in the brain appears as the final stage. In these cases, acute exacerbations are likely to occur with serious destruction of bronchopulmonary tissues. At these times, there are cough and expectoration of foul-smelling sputum containing the characteristic organisms. This devastating process may be controlled by arsphenamine therapy.

The bronchial lesions observed in cases of gangrene coming to autopsy varied from simple mild inflammation of the mucous membrane to complete destruction of the bronchial wall. In portions showing the milder lesions the exudate in the lumen and in the wall showed nothing characteristic except the presence of the Miller-Vincent organisms. In the more advanced cases the ulceration of the mucosa and the destruction of elastic tissue and even cartilage are characteristic, and the Miller-Vincent organisms are numerous. In some cases, there was complete necrosis of portions of the bronchial wall, with similar involvement of the regional parenchymatous tissue. The cavity formed thereby was a bronchopulmonary rather than a true bronchiectatic cavity. Some of the involved bronchi showed definite evidence of variable dilatation, with small, irregularly distributed, recent or old ulcerations of the wall. Such lesions readily harbor the Miller-Vincent organisms and permit the formation of whole colonies, which compose the whitish and yellowish balls expectorated in cases of bronchitis and bronchiectasis. In the eight cases of bronchitis with the Miller-Vincent organisms the lesions were doubtless similar to those observed in cases of pulmonary gangrene.

Miller-Vincent's Infection of the Pleura.—The symptoms in cases of Miller-Vincent's infection of the pleura are essentially those of any pleuritis, the differential diagnosis being made after thoracentesis.

In many cases of both acute and chronic pulmonary gangrene the pleura became involved, this complication not infrequently eventuating in pyopneumothorax. More commonly, associated with the inflamed pleura, a gangrenous effusion was found. In some cases (the earlier ones in this series), thoracentesis was followed by gangrenous cellulitis of the wall of the chest. In one case, seen in consultation (S.S.B.), the gangrene of the wall of the chest extended not only over the chest but over the trunk and down to the thigh. Because of the danger of this complication, thoracentesis, if performed, should be followed promptly by resection of the ribs and free drainage of the pleural cavity, permitting free communication with the air. This procedure, with energetic specific treatment, has resulted favorably when the condition seemed hopeless.

In two cases in this series, both in men, gangrenous pleurisy was present without appreciable involvement of the lung. In one case this condition complicated pneumonia, which apparently was minimal, but from which the process extended to the pleura. In the second case the condition followed a gunshot wound of the chest. In both cases the process eventuated in pyopneumothorax and the patients became desperately ill. The pleural contents were exceedingly foul-smelling and contained the characteristic organisms, which permitted a prompt diagnosis. Energetic treatment was instituted, followed by thoracentesis; wide resection was done, and arsenic therapy begun immediately, but in one case the patient died before more than one injection could be given. In the second, following repeated doses of arsphenamine, the patient recovered.

As shown in table 2, in many of the cases of pulmonary gangrene there was involvement of the pleura, and not uncommonly gangrenous effusion was present. In the cases observed at autopsy the pleural involvement varied from simple inflammation with little exudate containing the characteristic organisms, to lesions showing considerable infiltration of the pleural surfaces and the presence in the pleural cavity of large quantities of foul-smelling, thin, brown fluid containing innumerable Miller-Vincent's organisms. In some cases in which there were circumscribed lesions, fibrinous and fibrinopurulent exudate was present, and in the more chronic cases considerable organization of exudate with adhesions was observed.

PROGNOSIS

In this series, 96 per cent of the patients with embolic pulmonary abscesses died. The mortality in cases of bronchogenic abscess was 58 per cent. In contrast to these results are those in properly treated cases of pulmonary gangrene with cavitation, a much more severe

process than pyogenic abscess. In twenty-five such cases the mortality was only 32 per cent. The mortality in the whole group of cases of gangrene, including fourteen in which no arsenic treatment or one treatment was given when the patient was moribund (within four days of death), was 49 per cent.

ORGANISMS OF MILLER-VINCENT'S INFECTION

The spirochetes, fusiform bacilli and vibrios of pulmonary infections are identical with those occurring in the mouth. The first careful description of the spirochetes present in the mouth between the gums and the teeth was that of Miller,[5] in 1890. In addition to the small, slender Spirochaeta dentium described by Koch in 1877, he observed larger forms (apparently identical with Spirochaeta vincenti and Treponema macrodentium) associated with a comma bacillus (Spirillum sputigenum, identified by subsequent investigators as Vibrio proteus). The spirochetes are motile anaerobes from 4 to 15 microns long with from two to twenty irregular coils. In smears they are gram-negative. The vibrio is a motile aerobe with a number of flagellae, curved, gram-negative, from 2 to 5 microns long and about 1 micron thick. The fusiform bacillus, first described as an inhabitant of the mouth by Vincent[6] in 1899, is an anaerobe, nonmotile, straight, spindle-shaped, pointed at the ends, somewhat variable in its absorption of Gram's stain (smaller forms are gram-positive, and large forms, gram-negative), from 3 to 10 microns long and about 0.5 micron thick.

Plaut,[7] in 1894, and Vincent,[8] in 1896, pointed out the relationship of these organisms to the angina that bears their names. Plaut ascribed the angina to the Miller organisms (oral spirochetes and vibrios), and Vincent, to a spirochete and the fusiform bacillus.

Since the observations of Plaut and Vincent, the three types of organism—oral spirochetes (Miller), vibrios (Miller) and fusiform bacilli (Vincent)—have been found present not only in angina but in ulcerative gingivitis, dental caries, noma, pulmonary gangrene, gangrenous balanitis and gangrenous vulvitis. The color in gangrene in all likelihood is due to hemorrhage and to alteration of the blood, and the odor to substances produced in the lesion by the bacteria, especially by the vibrios.

The vibrio, although aerobic, motile, flagellated, curved and gram-negative, has been confused with the fusiform bacillus. Furthermore, although it is generally believed that the spirochete and the fusiform

5. Miller, W. D.: The Micro-Organisms of the Human Mouth, Philadelphia, S. S. White Dental Manufacturing Company, 1890, p. 80.
6. Vincent, M. H.: Ann. Inst. Pasteur **13**:609, 1899.
7. Plaut, H.: Deutsche med. Wchnschr. **49**:920, 1894.
8. Vincent, M. H.: Ann. Inst. Pasteur **10**:488, 1896; **13**:609, 1899.

TABLE 2.—*Cases of Pulmonary Abscess and of Pulmonary Gangrene at Mount Sinai Hospital, July 1923 to July 1933*

	Number of Cases	Sex		Age		Complicating Bronchitis or Pneumonia	Postoperative		No Anesthesia	Location*					Arsenic Treatment		No Arsenic Treatment†		Postmortem Examination
		M	F	Infants and Children	Adults		General Anesthesia	Local Anesthesia		RU	RM	RL	LU	LL	Recovered	Died	Recovered	Died	
Staphylococcic bacteremia or pyemia with embolic pulmonary abscesses	23	..	..	14	9	..	..	..	..	..	..	..	..	..	..	..	1	22	16
Pulmonary abscess (bronchogenic)	12	10	2	8	4	8	8 (1 oral operation)	1 (nonoral operation)	..	2	1	2	2	4	..	..	5	7	4; 1 associated with bacteremia caused by B. pyocyaneus
Miller-Vincent's pulmonary infection (pulmonary spirochetosis)																			
Gangrene.....	39	25	14	7	32	17	17 (8 oral operations)	4 (2 oral operations)	1 (oral operation)	14	7	18	6	15	17	8	3‡	11	10
Pneumonitis.....	6	4	2	0	6	4	1 (nonoral operation)	..	1 (oral operation)	1	0	4	1	3	6	..	..	..	..
Bronchitis.....	8	7	1	0	8	..	..	..	..	5	2	4	4	4	6	1§	1	..	0
Pleurisy.....	2	2	0	0	2	1	1 (following gunshot wound)	..	..	..	..	..	..	2	1	..	..	1	0
Total Miller-Vincent's infection.....	55	38	17	7	48														
Grand total.....	90																		

* The abbreviations for location are: RU, the upper lobe of the right lung; RM, the middle lobe of the right lung; RL, the lower lobe of the right lung; LU, the upper lobe of the left lung, and LL, the lower lobe of the left lung.

† Some patients in this group received one treatment within four days of death.

‡ One was discharged the day after admission to the hospital.

§ There was active tuberculosis in the upper lobe of each lung.

bacillus live in symbiosis, there is no evidence in cultures that the presence of one favors the growth of the other, and, rather than one anaerobe favoring the growth of another in an aerobic environment, it is more likely that the vibrio, with its striking avidity for free oxygen (forming a surface pellicle in broth culture), is the symbiotic agent making possible the growth of the anaerobic oral spirochetes and anaerobic fusiform bacilli in the mouth and elsewhere.

The presence of spirochetes and fusiform bacilli in pulmonary gangrene was first reported in 1905 by Rona,[9] who believed not only that these organisms produced the gangrene but that carious teeth were their source. Supporting these observations are those of Buday,[10] reported in 1910. In a study of thirty-five cases of bronchial, bronchopulmonary and pulmonary gangrene, Buday found innumerable spirochetes, fusiform bacilli and comma bacilli in the involved areas. In the bronchial lesions, the fusiform bacilli and comma bacilli were present in larger numbers than the spirochetes. In the gangrenous areas of the lungs, however, the spirochetes predominated, innumerable organisms of this type being present not only in the necrotic tissue but also at the margins toward the intact portion of the lung. From a careful microscopic study of his cases, Buday concluded that in acute bronchogenic gangrene of the lung, spirochetes, fusiform bacilli and comma bacilli are, in the majority of cases, the causative agents and not secondary invaders.

More important in establishing the etiologic relationship of these organisms to gangrene than their presence in early gangrenous areas and at the margin of more advanced ones is the fact that, with material containing them, similar lesions have been produced in animals (Veszpremi;[11] Loygue, Bonnet and Peyre;[12] Kline;[13] Pilot and Davis;[14] Smith[15]). Furthermore, Smith,[16] with combined pure cultures of T. microdentium, an anaerobic hemolytic streptococcus, a small fusiform bacillus and a vibrio, succeeded in producing the lesion in rabbits after passage of the combined organisms through mice and guinea-pigs.

9. Rona, S.: Arch. f. Dermat. u. Syph. **74**:171, 1905.

10. Buday, K.: Beitr. z. path. Anat. u. z. allg. Path. **48**:70, 1910.

11. Veszpremi, D.: Centralbl. f. Bakt. (Abt. 1) **38**:136, 1905; **44**:408, 1907; **45**:15, 1908.

12. Loygue, M. G.; Bonnet, H., and Peyre, E.: Bull. et mém. Soc. méd. d. hôp. de Paris **42**:1099, 1918.

13. Kline, B. S.: Experimental Gangrene, J. Infect. Dis. **32**:481, 1923.

14. Pilot, I., and Davis, D. T.: Studies in Fusiform Bacilli and Spirochetes, Arch. Int. Med. **34**:313 (Sept.) 1924.

15. Smith, D. T.: Experimental Aspiratory Abscess, Arch. Surg. **14**:231 (Jan.) 1927.

16. Smith, D. T.: Fuso-Spirochetal Disease of the Lungs Produced with Cultures from Vincent's Angina, J. Infect. Dis. **46**:303, 1930.

Case; Name; Sex	Color; Age; Date Admitted	Pulmonary Spirochetosis: Bronchitis	Pulmonary Spirochetosis: Pneumonitis	Pulmonary Spirochetosis: Gangrene	Location: Right Lung: Upper	Location: Right Lung: Middle	Location: Right Lung: Lower	Location: Left Lung: Upper	Location: Left Lung: Lower	Pleural Effusion	Mill Org Pleu
1 J. V. Male	White 38 9/24/23	..	..	+	+	+	+	+		+ 9/24, roentgenogram: effusion on right	10/27
					9/21, roentgenogram: fluid with infiltration above suggesting tuberculosis			9/24, roentgenogram: some infiltration; 9/26: localized pneumothorax			
2 L. J. Female	White 37 9/30/23	..	..	+			+	.....		.....	.....
					10/20, roentgenogram: moderate cloudiness in base; infiltration suggestive of abscess						
3 H. D. Male	White 32 11/10/23	..	.. Pleural		.....			+ 11/19, roentgenogram: fluid to second rib on left; 12/7, same; 12/21, pneumothorax; 1/17/24, same; no fluid		12/20: gangrenous pyopneumothorax on left	
4 J. E. Male	White 68 1/15/2	..	..	+	+		+	+		.....	
					2/24, postmortem examination			2/24, postmortem examination		200 cc. thin turbid faintly green-tinged somewhat foul-smelling fluid on right	
5 W. R. Male	White 30 3/1/24	..	+	..	+		+	.....		.....	.....
					3/1, roentgenogram: infiltration in upper and lower lobes suggestive of tuberculosis; 3/8: much less cloudiness, probably not tuberculosis; 3/15: practically complete disappearance of infiltration						
6 V. C. Male	White 29 3/28/24	+	..	..	+			+		.....	.....
					3/29, roentgenogram: suggestive of tuberculosis in both upper lobes						
7 G. K. Male	White 42 5/24/24	..	..	+		+	+	.....		.....	.....
					5/19, roentgenogram before admission: evidence of cavities in middle lobe						
8 J. A. Male	White 20 7/28/24	..	+	..			+	+	+	.....	.....
					Physical examination on admission: involvement of both bases			7/28, roentgenogram: several areas of increased density in upper lobe, some fine mottling in lower; bilateral			
9 W. P. Male	White 27 9/9/24	..	..	+	.....			+ 9/9, roentgenogram: abscess in base of upper lobe or interlobar empyema; 9/21, abscess in upper lobe		10/10: thick gangrenous pus, small amount	
10 M. M. Female	White 33 9/13/24	..	..	+	+			.....		.....	.....
					9/18, roentgenograms: infiltration in cavity of upper lobe; 10/10: less involvement						
11 J. H. Male	White 26 10/6/24	..	..	+	+			10/16, roentgenogram: fluid in right base		Postmortem examination: few hundred cc. serosanguinofibrinopurulent on right side; 60 cc. blood-tinged on left side	.....
					Postmortem examination: M-V in smear of pulmonary gangrene in upper lobe						
12 O. F. Male	White 60 11/1/24	+	..	..	.....			+	+	.....	.....
								11/3, roentgenogram: bilateral bronchial thickening; some infiltration in base; some mottling in upper lobe			
13 T. S. Male	White 39 11/26/24	+	..	..	Bilateral; diffuse			.....		.....	.....
14 L. G. Male	White 55 11/26/24	+	..	+	+			+		.....	.....
					11/27, roentgenogram: diminished density in upper portion of each lung; 12/16: cavities in each upper lobe, apparently tuberculous						
15 J. S. Male	White 29 3/1/25	..	+	+?	.....			+ 3/2, roentgenogram: pneumonitis (?); fluid; 3/26: less cloudiness and thickened pleura (?)		3/19: gangrenous effusion, 13 oz. (373.5 cc.)	
16 C. L. Male	White 8 4/21/25	..	..	+	.....			+ 4/22, roentgenogram: fluid; 4/27: pyopneumothorax	+ 4/29: large quantity foul-smelling fluid		4/28-4 mera isms
17 R. N. Female	White 16 6/3/25	..	..	+		+		.....		+ 6/5: quantity (?) of foul-smelling pus	6/5: f bacill (no s grow lytic
					6/4, roentgenogram: cavity and fluid in middle lobe						
18 D. B. Male	White 31 3/10/26	..	..	+	.....			+ 3/11, roentgenogram: pyopneumothorax	+ 3/16: gangrenous		
19 P. W. Male	White 50 5/1/26	+	..	+			+	.....		.....	.....
					5/4, roentgenogram: bronchiectasis in base of both lungs; clinical signs of bronchopneumonia, especially in lower lobe; 5/10: same as on 5/4 except for cavity in the base						
20 H. S. Female	White 46 9/20/26	..	..	+			+	.....		.....	.....
					10/13, roentgenogram: cavity in lower lobe						
21 A. T. Male	White 39 5/7/27	..	.. Pleural		.....			+ Clinical signs of pyopneumothorax		.....	5/9, 5/ bacill spiroc
22 F. S. Male	White 50 5/28/27	..	..	+	+		+	+	+	+ 100 cc. serosanguineous in right side of chest; 1,000 cc. in left side of chest at autopsy	.....
					5/29, roentgenogram: no abnormalities in lungs; porstmortem examination: focal areas with innumerable M-V organisms in direct smears and sections of tissues			.....			

TABLE 3.—*Summary of Fifty-Fi*

	Miller-Vincent Organisms in Pleural Fluid	Following Bronchitis or Pneumonia	Following Operation with Anesthesia	Sputum (Gross Character)	Miller-Vincent Organisms* Washed Sputum	Oral Observations	White Blood Cells: Date	White Blood Cells: Count	White Blood Cells: Percentage of Polymorpho-
sion	+	+			+				
gram: t	10/27 drainage	Following cut on hand	.....	10/29: gray, foul-smelling	10/29: numerous	Erosions and cavities in teeth after admission	9/25	21,600	..
.....	.....	.....	10/10: general: tonsils, adenoids and carious teeth removed	Foul-smelling, blood-streaked a few weeks after tonsillectomy	11/16: moderate number	Teeth in good condition on admission; some found by roentgenogram to be abscessed	9/30 10/14	5,000 12,500	.. 78
ous rax	+ 12/24	Following gunshot wound in left lung	.....	Hemorrhage from mouth on admission; bloody in hospital; 12/20: brown, foul-smelling	.....	Teeth in fair condition	11/12 12/20	11,000 22,000	..
old nged n right	.....	.....	1/28/24: general: prostatectomy	2/21: yellow; breath foul	.....	Some teeth carious on admission; 2/24: M-V on postmortem examination	.....	.....	..
.....	.....	+	.....	Purulent before admission; no foul odor	+ 3/3: many	Teeth and gums in good condition	3/ 1	7,200	..
.....	.....	+	.....	Bloody from 6 to 8 months before admission	+ 4/11: numerous	4/26: teeth in good condition; tonsils large with crypts; breath putrid	.....	.....	..
.....	.....	+	.....	Green, gray, foul-smelling on admission	+ 5/25: numerous	Dental caries; thick, foul, green pus over pharynx	5/25	38,000	95
.....	.....	+	.....	Yellow, purulent, before admission	+ 7/29: moderate number	Teeth in good condition	7/28 7/31	15,500 16,250	..
gren-	+ 10/10	+	.....	Yellowish; occasionally blood-streaked for past 5 months	.....	Dental caries on admission; 10/24: M-V	9/ 9 9/17 9/24	14,300 12,100 9,550	59
.....	.....	.....	9/2: general: tonsillectomy	Foul sputum a few weeks after tonsillectomy	+ 9/18: numerous	9/18: numerous M-V in oral smear	.....	.....	..
amina- ed ce. rino- t side; ged on	.....	.....	10/6: general: appendectomy	.....	.....	Moderate pyorrhea on admission; 10/12: bad mouth; 10/23: M-V in oral smear	10/24	22,400	94
.....	.....	+	.....	Blood-tinged before admission	+ 11/3 and 5	Teeth poor; 12/5: M-V gingival smear	11/ 1 11/ 4 11/29 12/14 12/23 1/ 5	17,000 16,800 24,200 18,600 15,400 19,400	.. 78
.....	.....	+	.....	Yellowish, bloody, before admission	+ 11/28, 12/1, 12/5, none	Teeth in fair condition; 11/26: M-V in gingival smear	11/27	11,400	..
.....	.....	+ Superimposed on pulmonary tuberculosis	.....	Blood-tinged at onset; greenish in hospital; no characteristic odor	+ 11/29: few; 12/1: few fusiform bacilli several times	Marked gingivitis and pyorrhea on admission; 11/26: few M-V in gingival smear	11/29	17,600	..
s effu- 5 cc.)	+ 3/19	.....	+ 3/1/25: general: following appendectomy	Bloody fifth and sixth day after appendectomy	3/25, 3/26: none	3/21: M-V in gingival smear	3/ 1	18,150	..
tity id	+ 4/28-4/29: innumerable organisms	.....	+ General: tonsillectomy 2 weeks before admission	Foul-smelling	+ 4/29	4/28: M-V in smear from teeth; innumerable organisms	4/21	28,000	..
) of s	+ 6/5: fusiform bacilli and cocci (no spirochetes) growth nonhemolytic strep.	+	.....	Thick, foul-smelling, 10 days before admission	+ 6/4: fusiform bacilli gram-negative and gram-positive organisms including cocci; no spirochetes	Teeth in good condition	.....	.....	..
s	+ 3/16	+	.....	No description	+ 3/13, 15, 16	Dental caries on admission	3/ 6	24,900	..
.....	.....	+	.....	Profuse expectoration for one year (heavy, thick)	+ 5/6, 10, 13: in hard balls; 5/8, 12, 15, 20	5/5: teeth in poor condition on admission; moderate pyorrhea	5/ 2	12,200	..
.....	.....	+	.....	Purulent, brown few weeks before admission with M-V organisms; abundant, very foul, green on admission	+ 9/20, 10/3, 12, 13	Pharyngitis, sordes, teeth in fair condition	9/22 10/21	21,500 20,000	..
.....	+ 5/9, 5/11: fusiform bacilli, few spirochetes	+	.....	No description	Diagnosis from pleural fluid	Marked pyorrhea on admission	5/ 7	24,000	84
ineous hest; dde psy	.....	.....	+ 5/31: general: extraction of teeth and alveolectomy	6/8: black phlegm, yellow mucus; 6/10: bloody mucus	+ 6/10: few spirochetes	5/29: teeth in poor condition; some recently extracted; marked pyorrhea	5/28 5/31 6/ 2 6/ 3 6/ 4 6/ 5 6/ 6 6/ 7 6/ 8 6/ 9 6/12	20,000 13,000 10,000 1,650 1,250 750 800 420 400 330 270	8 9 6 20 50 50

White Blood Cell Count								
	Date	Count	Percentage of Polymorphonuclears	Percentage of Lymphocytes	Percentage of Monocytes	Temperature	Treatment with Arsenic	Duration	
ns - r	9/25	21,600	..	..	..	100 F. on admission; 9/26: 102 F.; about 100 F. throughout; sometimes normal, sometimes 102 F.; 100 F. at death	10/27: 0.6 Gm. neoarsphenamine	11 mo.	.....
n- m	9/30 10/14	5,000 12,500	.. 78	..	..	96 F. on admission to 98 F. same day; normal to day following tonsillectomy then to 101 F.; 100 to 103 F. for week; 10/21: normal. Irregular for one week then to 102 F. on 11/2. About 102 F. for one week, gradually falling to normal on 11/25, after second injection of neoarsphenamine; 99 F. on discharge	11/16: neoarsphenamine; 11/23: 0.6 Gm.	7½ wk.	Renal calc pyelitis
	11/12 12/20	11,000 22,000	..	..	..	99 F. on admission, rising to 102 F. in 32 hours; about 100 to 101 F. for weeks, occasionally higher or lower. Normal 12/29, remaining so with few exceptions	12/27: 0.4 Gm. neoarsphenamine; 1/4/24: 0.4 Gm.; 1/10: 0.6 Gm.; 11/11: transfusion of 600 cc. of blood	3 mo.	.....
us 24: tem	.....	.....	..	..	..	101.5 F. day following operation; remittent, then intermittent; 102 F. highest	0	4 wk.	Hypertrop
in	3/ 1	7,200	..	..	..	99.6 F. on admission; slight change throughout; p. m. rise not above 99.4 F.; subnormal at times; 98 F. on discharge	3/4: 0.5 Gm. sulpharsphenamine intramuscularly; 3/9: 0.45 Gm. intramuscularly	4 wk.	.....
od s ;	.....	.....	..	..	..	Dispensary case; 3/28 and 4/26 no elevation	4/30: 0.2 Gm. arsphenamine intravenously; 5/14 and 28: 0.5 Gm.; 6/4: 0.5 Gm. neoarsphenamine; 6/11: 0.5 Gm. sulpharsphenamine intramuscularly	7 to 9 mo.	.....
x	5/25	38,000	95	..	..	103 F. on admission; then intermittent, 99 to 102 F.; 100.4 at death	5/25 and 27: 0.6 Gm. neoarsphenamine	3½ wk.	.....
n-	7/28 7/31	15,500 16,250	..	..	..	103.4 F. on admission; normal on following day; normal thereafter; 98 F. on discharge	8/2: 0.4 Gm. neoarsphenamine; 8/6: 0.6 Gm.; 4 weekly injections beginning 8/8 (6 injections)	16 da.	.....
	9/ 9 9/17 9/24	14,300 12,100 9,550	59	40	..	100 F. on admission; increased to 103 F. on sixth day; to 99 F. after eighth day; not over 100 F. for 11 days; irregularly intermittent as high as 102 F. for few weeks; about normal for few weeks before discharge; 98 F. at discharge	9/12: 0.4 Gm. sulpharsphenamine intramuscularly; 10/15, 18 and 27, 11/3: 0.6 Gm. neoarsphenamine	6 mo.	.....
ar	.....	.....	..	..	..	104 F. 13 days following tonsillectomy; remained here several days then fell gradually to normal (3 weeks following first sulpharsphenamine injection)	9/18, 23 and 28, 10/2: 0.5 Gm. sulpharsphenamine intramuscularly	1 mo.	.....
hea h; al	10/24	22,400	94	..	..	103 F. on admission; remained at 100 to 103 F.; about 102 F. last 10 days; 103.5 F. at death	10/25: 0.4 Gm. arsphenamine intravenously	2 wk.	Pulmonary lower lobe thrombosis
5: ear	11/ 1 11/ 4 11/29 12/14 12/23 1/ 5	17,000 16,800 24,200 18,600 15,400 19,400	.. 78	..	..	98.4 F. on admission; no elevation; usually 97 to 98 F.; 97.5 on discharge	11/7: 0.3 Gm. sulpharsphenamine intramuscularly; 11/10 and 13, 12/2: 0.4 Gm.	7 yr.	Polycythem
n- V ar	11/27	11,400	..	..	..	98.4 F. on admission; no elevation; at times subnormal	12/4: 0.6 Gm. neoarsphenamine	2 yr.	Mitral sten (chronic br
is n s:	11/29	17,600	..	..	..	99.2 F. on admission; about 100 F. throughout; as high as 101.5 F.; 99.5 F. on discharge	11/30: 0.45 Gm. neoarsphenamine; 12/6, 12, 18 and 26: 0.6 Gm.	1 yr.	27th exami itive result Wasserman ilis; pulm upper lobes
-	3/ 1	18,150	..	..	..	100.2 F. on admission; fell day after appendectomy to normal, rose fifth day postoperatively to 100 F., then from 100 to 101 F. for 10 days (occasionally 102 F.). Fell immediately after thoracostomy from 103 F. to normal, remained normal 3 days then about 100.5 F. 5 days. 99.5 F. on discharge	3/23: 0.4 Gm. neoarsphenamine; 3/26: 0.6 Gm.	3 wk.	.....
ear - ms	4/21	28,000	..	..	..	103.6 F. on admission; 101 to 104 F. for 9 days. Following injection of arsenic and resection of rib, fell to about normal 1 day, then 102 to 100 F. for few weeks. About normal from 5/18 to discharge	4/28: 0.2 Gm. neoarsphenamine; 5/1: 0.3 Gm.; 5/4: 0.25 Gm. sulpharsphenamine; 5/8 and 12: 0.3 Gm.	9 to 10 wk.	.....
on-	.....	.....	..	..	..	101.4 F. on admission; fell in few days to normal. After operation elevated (100 to 102 F.) for several days falling gradually to normal 6/13, remaining so until discharge	0	4 wk.	.....
	3/ 6	24,900	..	..	..	103 F. on admission; 100 to 103 F. for 11 days, then gradually to normal on sixteenth day, remaining so until discharge, 26 days after admission	3/15: 0.3 Gm. neoarsphenamine; 3/19: 0.45 Gm.; 3/24 and 29: 0.6 Gm.	5 wk.	.....
r	5/ 2	12,200	..	..	..	100.2 F. on admission, slightly irregular, occasionally subnormal; reached 101 F. one day, 102 F. another day, generally about normal	5/8, 14 and 20: 0.45 Gm. neoarsphenamine	1 yr.	Several in pleural cav of lung ob
	9/22 10/21	21,500 20,000	..	..	..	102 F. on admission, to normal in 5 days; 99 to 100.5 F. for 10 days; then about 100 F.; 100 to 102 F. after operation; 100.5 F. at death	2 injections of neoarsphenamine before admission; 9/21: 0.6 Gm.	7 wk.	.....
a	5/ 7	24,000	84	..	..	Onset 1½ weeks before admission with chills, fever, cough, pain in left side of chest. Temperature on admission, 103.7 F., gradually fell to 100 F., once to normal, 99.7 at death	5/11: 0.45 Gm. neoarsphenamine	2 wk.	.....
or d; a	5/28 5/31 6/ 2 6/ 3 6/ 4 6/ 5 6/ 6 6/ 7 6/ 8 6/ 9 6/12	20,000 13,000 10,000 1,650 1,250 750 800 420 400 3 2	5 9 6 26	95 90 90	..	98 F. on admission; rose after extraction of teeth and alveolectomy, reaching 104 F. on 6/3. Remained elevated, 103 F. at death; a few days before death as low as 100.2 F.	0	11 da. postoperatively	.....
	Male		5/1/26				both lungs; clinical signs of bronchopneumonia, especially in lower lobe; 5/10: same as on 5/4 except for cavity in the base		
	20 H. S. Female	White 46 9/20/26	..	..	+	10/13, roentgenogram: cavity in lower lobe	+	.....	.....

Other Conditions	Discharged	Cured or Improved	Additional Data and Follow-Up	Died	Postmortem Examination
.....	10/29	..	9/29: resection of rib; large amount of foul-smelling pus removed from pleural cavity	+	0
Renal calculus in left kidney; chronic pyelitis	12/2	I	4/28/25: in good health. Roentgen examination: slight cloudiness in right upper chest, otherwise normal. 2/8/33: occasional hoarseness and cough; gained weight; general condition good; physical findings in chest normal. X-ray findings (chest) 2/8/33: there is considerable thickening in both hili extending along lower bronchial trees; no definite foci of recent parenchymatous infiltration	..	..
.....	2/3/24	I	12/14/23: resection of rib. 12/24/23: drainage material from thoracostomy wound foul-smelling, containing M-V. 4/28/25: weight regained; roentgenogram normal except for thickening on left side	..	..
Hypertrophy of prostate.....	2/23	..	.....	+	+ 2/24
.....	3/15	C	6/1/33: in good health.....	..	..
.....	6/11	I	.....	..	..
.....	5/28	..	.....	+	0
.....	8/6	C	5/5/25: roentgen examination: lungs clear.....	..	..
.....	11/5	I	10/10: resection of rib.....	..	..
.....	10/10	C	4/25/25: roentgen examination: lungs clear.....	..	..
Pulmonary embolism and infarcts in lower lobe of right lung following thrombosis left iliac vein	10/25	..	10/16: thoracentesis right side, no result; 10/24: thoracentesis, no result.....	+	+
Polycythemia (Vaquez's disease).....	11/13	I	5/25/25: roentgen examination: generalized peribronchial thickening; no infiltration	..	..
Mitral stenosis; pulmonary congestion (chronic bronchitis)	12/5	I	12/4: nausea, weakness, vomiting after 0.6 Gm. of neoarsphenamine.....	..	..
27th examination of sputum gave positive results for B. tuberculosis; 11/28: Wassermann ++++ for latent syphilis; pulmonary tuberculosis both upper lobes with cavitation	12/30	I	Died several months later at City Hospital of pulmonary tuberculosis.....	..	..
.....	3/28	I	3/19: resection of rib; 3/26: thoracentesis with no result.....	..	..
.....	6/17	C	4/28: thoracentesis, 110 cc. foul-smelling thin pus; 4/29: resection of rib (local anesthesia)	..	..
.....	6/20	I	6/5: resection of rib (local anesthesia).....	..	..
.....	4/4	I	3/13: thoracentesis, 120 cc. fluid; 3/15: thoracentesis, no result; 3/16: thoracentesis of left side, 800 cc. fluid; 3/17: resection of rib (pus obtained by thoracentesis)	..	..
Several injections of air into right pleural cavity; no appreciable collapse of lung obtained	6/3	Unimproved	.....	..	..
.....	10/24	..	2 days after injection of 0.6 Gm. neoarsphenamine, pain in arm and fingers, generalized eruption (morbilliform macular, maculopapular); 10/21: resection of rib (local anesthesia)	+	0
.....	5/12	..	3 days before admission, thoracentesis, yellow pus obtained; 5/9 and 11: thoracentesis, abundant foul-smelling, purulent fluid; 5/10: phlegmonous cellulitis in left lower side of chest; 5/12: incision and drainage of abscess in wall of chest	+	0
.....	6/11	..	.....	+	+

			(heavy, thick)	15, 20		mission; moderate pyorrhea			
.....	.....	+	.....	Purulent, brown few weeks before admission with M-V organisms; abundant,	9/20, 10/3, 12, 13	+	Pharyngitis, sordes, teeth in fair condition	9/22 10/21	21,500 20,000	..

6/ 7	420							
6/ 8	400							
6/ 9	3							
6/12	2							
	Male 5/1/26				both lungs; clinical signs of bronchopneumonia, especially in lower lobe; 5/10: same as on 5/4 except for cavity in the base			
20 H. S. Female	White 46 9/20/26	..	..	+	+ 10/13, roentgenogram: cavity in lower lobe	.....	.....	..
21 A. T. Male	White 39 5/7/27	..	..	Pleural	.....	+ Clinical signs of pyopneumothorax	.....	5/ b sp
22 F. S. Male	White 50 5/28/27	..	..	+	+ 5/29, roentgenogram: no abnormalities in lungs; porstmortem examination: focal areas with innumerable M-V organisms in direct smears and sections of tissues	+ ..... +	+ 100 cc. serosanguineous in right side of chest; 1,000 cc. in left side of chest at autopsy	..
23 K. L. Female	White 32 6/21/27	..	+	..	7/9, roentgenogram: slight cloudiness in lower lung field	+ 6/27, roentgenogram: moderate diffuse cloudiness; 7/9: more localized; 8/5: infiltration greatly diminished	.....	..
24 R. K. Female	White 25 8/6/27	..	..	+	+ 8/7, roentgenogram: cavity; 9/6: cavity smaller	.....	.....	..
25 B. M. Female	Colored 26 8/14/27	..	..	+	+ 9/26, roentgenogram: large cavity in lower lobe	+ 9/26, roentgenogram: irregular area of infiltration in lower lobe; 9/30: beginning necrosis in lower	+ 9/24: pyopneumothorax, gangrenous effusion	
26 S. S. Male	White 51 10/3/27	..	..	+	.....	+ 10/4, 10/22, 11/11, roentgenogram: cavities	+ Left	..
	52 2/23/28	..	..	+	.....	+	.....	..
27 G. W. Male	Colored 28 11/22/27	..	..	+	+ Postmortem examination; no roentgen study +	+	+ 200 cc. and 300 cc. of thin straw-colored fluid on left side	..
28 M. W. Male	White 4 11/25/27	..	..	+	.....	+ No roentgen study; physical signs of cavity with gurgling sounds; bronchial breathing	.....	..
29 I. L. Female	White 42 11/27/27	..	..	+ Early	.....	+ 12/10, roentgenogram: areas of diminished density; early necrosis (disappeared 12/23)	.....	..
30 G. S. Male	White 43 12/3/27	..	..	+	.....	+ 12/19, roentgenogram: numerous areas of diminished denstiy; gangrene of lower lobe at autopsy	.....	..
31 M. G. Male	White 43 2/6/28	..	..	+	2/21: cavity in upper lobe.....	+ 2/7 and 13, roentgenogram: miliary tuberculosis with focus in lower lobe; 2/21: cavity in lower lobe	+ Gangrenous; 100 cc. from left side	A
32 Y. T. Female	White 8 2/12/28	..	..	+	+ +? + 2/23, roentgenogram: pneumonitis in upper lobe; gangrene in several lobes at autopsy	+	Local pleurisy, 100 cc. clear fluid from right side	..
33 G. S. Female	White 26 3/10/28	..	..	+	+ 3/25: physical signs of pneumonia in lower lobe; 6/9, roentgenogram: moderate effusion in right base; 7/17, roentgenogram: old empyema; 8/24: fluid in base on each side	+ 6/9, roentgenogram: slight effusion; 9/20: abscess or early bronchiectatic cavity	6/15: pus obtained, innumerable, small, gram-negative bacilli, gram-positive cocci, growth of Str. haemolyticus	..
34 J. S. Male	White 54 3/17/28	..	..	+	+ 3/19, roentgenogram: necrosis..... +	.....	.....	..
	6/9/28	+	..	..	+ 6/11, roentgenogram: ring shadows in lower lobe of each lung	+	.....	..
35 M. N. Male	White 41 4/13/28	+	..	..	+ 4/14, roentgenogram: pneumonia with effusion in right base; 5/14: thickened pleura	.....	+	..
	6/14/28	..	..	..	+ 7/10, roentgenogram: encapsulated empyema	.....	Drainage of pus	..
	3/29/29	..	..	..	.....	.....	Drainage of pus	..
	11/12/29	..	..	..	11/14, roentgenogram: old resection of ninth, tenth and eleventh ribs	....	Drainage of pus	..
	5/20/31	..	..	..	.....	.....	Drainage of pus	..
36 J. P. Male	White 62 5/11/28	..	..	+	+ 5/12, roentgenogram: necrosis.....	.....	.....	..
37 S. S. Female	White 42 7/3/28	..	..	+ Early	.....	+ 7/11, roentgenogram: suggestive of cavity; 7/30: less signs	.....	..
38 S. S. Male	White 40 8/3/28	..	..	+	+ 8/4, roentgenogram: necrosis..... +	.....	.....	..
10/21	20,000	..	..	..	100.5 F. for 10 days; then about 100 F.; 100 to 102 F. after operation; 100.5 F. at death	before admission; 9/21: 0.6 Gm.		

				(heavy, thick)	15, 20	condition on admission; moderate pyorrhea			
		+		Purulent, brown few weeks before admission with M-V organisms; abundant, very foul, green on admission	+ 9/20, 10/3, 12, 13	Pharyngitis, sordes, teeth in fair condition	9/22 10/21	21,500 20,000	
	+ 5/9, 5/11: fusiform bacilli, few spirochetes	+		No description	Diagnosis from pleural fluid	Marked pyorrhea on admission	5/ 7	24,000	84
anguineous of chest; ft side utopsy			+ 5/31: general: extraction of teeth and alveolectomy	6/8: black phlegm, yellow mucus; 6/10: bloody mucus	+ 6/10: few spirochetes	5/29: teeth in poor condition; some recently extracted; marked pyorrhea	5/28 5/31 6/ 2 6/ 3 6/ 4 6/ 5 6/ 6 6/ 7 6/ 8 6/ 9 6/12	20,000 13,000 10,000 1,650 1,250 750 800 420 400 330 270	5 9 6 26 50 50
				Foul for several weeks before admission: occasionally blood-streaked after admission	+ 6/29, 7/9, 13, 15, 17, 19, 20, 22, 25, 8/1, 2, 5	Teeth fair; breath fetid	6/27 7/ 5 7/ 9 7/20	14,400 20,000 13,800 12,900	82
				Profuse, foul-smelling on admission	+ 8/11, 13, 17, 22, 27, 9/1	8/6: marked gingivitis, dental caries	8/ 7 8/26	15,000 8,600	
umo-grenous	+ 9/24		+ 8/14: general: laparotomy for separation of adhesions (intestinal obstruction)	9/21: greenish-yellow; 9/22, 9/24: very foul-smelling	9/18, 29	8/14: slight nasopharyngeal discharge	8/14 9/20	4,000 24,000	
t		+		10/5: foul-smelling	+ 10/4, 5, 10, 17, 25, 27, 11/4, 5, 7, 16, 17, 12/28	Teeth carious, pyorrhea	10/ 3 10/17 10/28 11/15	16,400 21,200 18,400 11,650	81
		+		2/23: profuse, greenish, foul-smelling	+ 2/24, 28, 3/2, 6, 4/18	Tongue coated, breath bad	12/ 6 2/23	7,600 6,200	48
0 cc. of olored side			+ 11/22: general: laparotomy for gunshot wounds	12/4: thin, white-green; 12/9: bloody	+ 12/8, 9	11/22: teeth dirty and carious	11/22	12,200	
			General: tonsillectomy; symptoms 2 weeks later	Foul odor few weeks after tonsillectomy; thick, green, occasionally blood-tinged	+ 11/25 and 26	Examination unsatisfactory	11/22	11,000	85
			11/28: local: ventral herniorrhophy	12/5 and 27: thick, yellow, blood-streaked	+ 12/9 and 10	Teeth carious on admission; 12/11: M-V in gingivitis and pyorrhea	11/27	6,800	
			12/3: general: perforated gastric or duodenal ulcer; 12/12: local: resuture of abdominal incision	12/16: foul; 12/18: brownish	+ 12/8, 20 and 23	Teeth dirty and carious on admission; M-V at autopsy in gingival exudate	12/ 3 12/19	11,300 15,000	
; 100 cc. e	+ At autopsy	+		Blood in sputum on admission and on 2/16; foul-smelling	+ 2/7, 9, 11 and 15	Gingivitis and pyorrhea on admission; 2/16 and 20: M-V	2/ 6 2/14 2/22	19,500 27,300 9,870	79
y, 100 cc. om			2/12: general: incision and drainage, osteomyelitis of the mandible (2½ oz. foul pus evacuated); 2/26: several teeth extracted	2/16: breath foul; no description of sputum		2/15: osteomyelitis of the mandible; gangrenous stomatitis with M-V	2/12	10,000	
tained, , small, ve bacilli, e cocci, r.			3/10: general: appendectomy, bilateral salpingectomy, right oophorectomy	9/17: green, foul	+ 6/13: B. fusiformis and vibrios; 9/17: many M-V	Teeth good condition on admission	3/10 3/13 3/25 7/ 2	21,000 10,400 12,400 13,300	
			2/29: local: insertion of 5 radon seeds in carcinoma of larynx; 3/21: teeth extracted	Much, foul-smelling on admission	+ 3/19, 20, 21, 23, 27 and 28, 4/23	Marked pyorrhea; teeth bad	3/17	11,400	74
		Following pulmonary spirochetosis		Abundant, occasionally bloody	+ 6/12		6/ 9	8,200	
		+ Present admission exacerbation (?)		Thick, yellow occasionally blood-streaked	+ 4/26, 5/8, 9, 14	Teeth in good condition	4/14 4/29 5/18	15,750 25,400 22,000	82 79
pus					+ 6/15, 21: B. fusiformis and vibrios		6/14 7/18 8/ 1	19,200 14,550 14,200	
pus						Moderate number of M-V in oral smear	3/30	13,300	
pus				12/3: yellow mucopus, no M-Vs; 12/4: much blood, no M-V			11/13 11/30	10,600 6,200	
pus				6/8: mucopurulent		Teeth fair	5/20 5/31 6/12 7/ 1	19,800 18,400 14,600 11,600	
		+		Sputum beginning 6 or 7 weeks before admission; foul odor to breath	+ 5/12, 16	Gums and teeth in poor condition	5/12	13,800	76
		+	6/21 and 23: local; teeth extracted	Foul-smelling, beginning 6 days before admission	+ 7/5, 6, 11, 12, 13, 14, 17, 18 and 20	Marked gingivitis	7/ 3 7/ 7 7/25	11,200 8,800 9,000	73
		+		Foul-smelling, beginning 1 week before admission	+ 8/4: fusiform bacilli and vibrios, no spirochetes; 8/11, 12, 15 and 18: spirochetes	Gums and teeth in poor condition, tongue sore	8/ 3	21,950	73

generalized eruption (morbilliform macular, maculopapular); 10/21: resection of rib (local anesthesia)

S. S. Male	40	8/3/28			8/4, roentgenogram: necrosis			
	10/21	20,000	..	..	..	100.5 F. for 10 days; then about 100 F.; 100 to 102 F. after operation; 100.5 F. at death	before admission; 9/21: 0.6 Gm.	
	5/ 7	24,000	84	..	..	Onset 1½ weeks before admission with chills, fever, cough, pain in left side of chest. Temperature on admission, 103.7 F., gradually fell to 100 F., once to normal, 99.7 at death	5/11: 0.45 Gm. neoarsphenamine	2 wk.
	5/28	20,000	5	95	..	98 F. on admission; rose after extraction of teeth and alveolectomy, reaching 104 F. on 6/3. Remained elevated, 103 F. at death; a few days before death as low as 100.2 F.	0	11 da. post-operatively
	5/31	13,000	9	90				
	6/ 2	10,000	6	90				
	6/ 3	1,650						
	6/ 4	1,250						
	6/ 5	750	26					
	6/ 6	800						
	6/ 7	420						
	6/ 8	400						
	6/ 9	330	50					
	6/12	270	50					
	6/27	14,400	..	..	..	100.5 F. on admission; 100 to 101 F. for 9 days; 101-102.5 F. for 4 days; fell to normal in 1 week. Some elevation for a few days about 1 week later with return to normal on discharge	6/29: 0.45 Gm. neoarsphenamine; 7/3 and 7: 0.6 Gm.; 7/14, 18 and 24: 0.9 Gm.	2 mo.
	7/ 5	20,000	82					
	7/ 9	13,800						
	7/20	12,900						
	8/ 7	15,000	..	..	..	103.8 F. on admission, 99 F. following day; 99 to 101 F. for several days, then about 101 F. several days; about normal except for a few elevations for several hours only; once to 105 F.; normal at discharge	8/7, 10, 19 and 27 and 9/2: 0.45 Gm. neoarsphenamine	6 mo. (5 mo. before admission)
	8/26	8,600						
	8/14	4,000	..	..	..	99 F. on admission; about 101 F. after operation for 8 days, then about normal for a few weeks; elevation to 101 F. in course of 3 days, then to normal. From 9/16, 101 to 103 F. until death (about 102 F.); 101 F. at death	9/22, 24, 26, 28 and 30 and 10/2: 0.45 Gm. neoarsphenamine	4 wk.; began on 9/6 2 or 3 weeks after laparotomy
	9/20	24,000						
	10/ 3	16,400	81	..	..	104.4 F. on admission, 102 to 103 F. several days, then, following injection of arsphenamine, gradual fall, remaining at about 100 F. beginning 10/22. Normal or subnormal beginning 11/29	10/7, 11, 14 and 18: 0.45 Gm. neoarsphenamine; 10/21 and 25: 0.6 Gm.; 10/31, 11/5, 11, 18 and 27, 12/8 and 14: 0.9 Gm.	3 mo.
	10/17	21,200						
	10/28	18,400						
	11/15	11,650						
	12/ 6	7,600						
	2/23	6,200	48	..	..	Usually subnormal; elevations to as high as 103 F. Subnormal several weeks before discharge	2/27: 0.9 Gm. neoarsphenamine	8 mo.
	11/22	12,200	..	..	..	Signs of pneumonitis in base of left lung 11/29. Temperature on admission, 96 F., rose to 101 F. after operation. Constantly elevated until death 100 to 104 (around 101 F. at first, then 102 F.); 104 F. at death	0	11 da.
	11/22	11,000	89	..	..	100 F. on admission; normal next day	0	3 mo.
	11/27	6,800	..	..	..	99 F. on admission; signs of pneumonitis in base of left lung 11/29, temperature 103 F.; average 101 F. for few weeks, as high as 104.5 F. once. Normal 12/18, then not over 100 F. Normal on discharge	12/10: 0.6 Gm. neoarsphenamine; 12/16 and 23: 0.9 Gm.	3½ to 4 wk.
	12/ 3	11,300	..	..	..	12/18: involvement of middle lobe of right lung and lower lobe of both (slightly irregular temperature after inversion of gastric ulcer, 12/3) for 1 week; temperature 12/15, 101.5 F. then remittent and twice intermittent. 103 F. at death	12/18: 0.6 Gm. neoarsphenamine; 12/21: 0.9 Gm.	10 da. to 2 wk.
	12/19	15,000						
	2/ 6	19,500	79	..	..	103.5 F. on admission, normal in a few days, then gradual rise to 102 F. on 2/12, about 101 F. several days; from 100 to 99 F. until death	2/9: 0.6 Gm. neoarsphenamine; 2/13, 17, 21, 27, 3/2 and 5: 0.9 Gm.	5 wk.
	2/14	27,300						
	2/22	9,870						
	2/12	10,000	..	..	..	104 F. on admission, drop to normal in 24 hours, followed by rise to 101.5 F., drop to normal for 12 hours, then 101 to 102.5 F. until death	2/14 and 17: 0.225 Gm. neoarsphenamine; 2/19 and 22: 0.3 Gm.	2 wk.
	3/10	21,000	..	..	..	102 F. on admission, 103 to 104.5 F. for several days after operation, then about 102 F. for a week; 101 F. for several weeks with 100 F. for a month, then irregular, occasionally as high as 103 F. About normal first few weeks in August, then intermittent to 100, 101 and occasionally to 102 F. Slightly irregular and subnormal few weeks before discharge	0	6 mo.
	3/13	10,400						
	3/25	12,400						
	7/ 2	13,300						
	3/17	11,400	74	..	..	104 F. on admission, fell quickly (few days) to normal, then slightly irregular, not over 100.5 F. then normal or subnormal after injections of neoarsphenamine	3/20: 0.6 Gm. neoarsphenamine; 3/24, 28, 4/2, 8, 13 and 26: 0.9 Gm.	5 wk.
	6/ 9	8,200	..	..	..	Slight elevation for a few days after removal (local anesthesia) of cervical nodes, not over 101 F., then normal	6/20 and 25: 0.6 Gm. neoarsphenamine	Several months
	4/14	15,750	82	..	..	103.5 F. on admission, 104.5 F. 2 days later, then fell to about 100 or 101 F. for few weeks, then somewhat less, later slightly irregular, 99 F. on discharge	4/30, 5/11 and 14: 0.6 Gm. neoarsphenamine; 5/17: 0.9 Gm.	Over 4 yr.; exacerbation at present
	4/29	25,400						
	5/18	22,000	78					
	6/14	19,200	..	..	..	About 100 F. for one week but intermittent, somewhat lower beginning a few days after thoracostomy; slightly irregular with occasional rise over 100 F.; 97 F. at discharge	0	.....
	7/18	14,550						
	8/ 1	14,200						
	3/30	13,300	..	..	..	98.6 F. on admission; elevated for 6 days post-operatively, falling from 103 F.; slight thereafter; 97 F. on discharge	0	.....
	11/13	10,600	..	..	..	99.6 F. on admission; elevated for about 1 week beginning 3 days after incision, falling steadily from 103.5 F. to normal	0	.....
	11/30	6,200						
	5/20	19,800	..	..	..	102 F. on admission; irregular, usually slight, occasionally to 101 or 102 F.; 98 F. on discharge	0	.....
	5/31	18,400						
	6/12	14,600						
	7/ 1	11,600						
	5/12	13,800	76	..	..	99.5 to 100 F.	5/12 and 15: 0.9 Gm. neoarsphenamine	7 wk.
	7/ 3	11,200	..	..	..	101 F. on admission; fell to normal in 24 hours after injection of arsphenamine; slight elevation for few days; then 100 to 103 F. for several days, then 100 F. or less. Normal about 10 days before discharge	7/3, 6 and 10: 0.6 Gm. neoarsphenamine	6 wk.
	7/ 7	8,800	79					
	7/25	9,000						
	8/ 3	21,950	75	..	..	100.8 F. on admission; normal several days, then slightly irregular, not over 101 F., gradually falling after injection of arsphenamine to normal or subnormal	8/4, 6, 9 and 12: 0.6 Gm. neoarsphenamine; 8/15: 0.4 Gm.; 8/22 and 24: 0.2 Gm. sulpharsphenamine; 8/27 and 9/4: 0.4 Gm..	7 wk.
	11/ 2	11,500	81	Myelocytes	Moderate; 100 to 102 F. for few weeks, then gradually less for 5 weeks with rise to 103.5 F.	9/25, 10/6: 0.45 Gm. neoarsphenamine; 10/16: 0.6 Gm.	Few months	
	11/ 8	13,500	84					
25	White							

					ning 1 week before admission	cilli and vibrios, no spirochetes; 8/11, 12, 15 and 18: spirochetes	poor condition, tongue sore
					generalized eruption (morbilliform macular, maculopapular); 10/21: resection of rib (local anesthesia)		+ 0
2 wk.		5/12	..	3 days before admission, thoracentesis, yellow pus obtained; 5/9 and 11: thoracentesis, abundant foul-smelling, purulent fluid; 5/10: phlegmonous cellulitis in left lower side of chest; 5/12: incision and drainage of abscess in wall of chest			+ 0
1 da. postoperatively		6/11	..				+ +
2 mo.		8/8	I gangrene arrested	Pulmonary condition followed opening of peritonsillar abscess (twice; no anesthesia) early in June; 7/24: frontal headache, nausea, pain in epigastrium, vomiting after injections of neoarsphenamine; symptoms disappeared in 5 days after 5 grains (0.975 Gm.) t. i. d. sodium thiosulphate treatment and 21 cc. of a 10 per cent solution intravenously			.. ..
mo. (5 mo. before admission)		9/10	I	Pulmonary condition followed childbirth; some ether inhaled; gangrene arrested at time of discharge; later, operation for obliteration of cavity followed by gradual down-hill course and death 8 months later			.. ..
wk.; began n 9/6 2 or 3 eeks after aparotomy		10/4	..	9/20: thoracentesis (right), thin pus aspirated; 9/24: multiple thoracenteses (right), 60 cc. thin pus; 9/29: cellulitis in wall of chest 6 cm. in diameter (region of puncture)			+ 0
3 mo.		12/30	I				.. ..
8 mo.		4/20	I	3/26: left phrenicectomy; general anesthesia			.. ..
11 da.	Multiple gunshot wounds in abdomen and forearm; perforations of the ileum and cecum; multiple abscesses in the abdominal cavity, some with spirochetes, fusiform bacilli; (chancre 7 years before with some antisyphilitic treatment)	12/9	..				+ +
3 mo.		11/26 (day after admission) unimproved	..	2/1/33: periodic attacks of cough, fever, expectoration of pus every 4 or 6 weeks; bronchoscopic treatments until 1931, since which time patient has been well, except that he takes cold easily. Physical examination revealed impaired resonance in base of left lung and axillary area, crepitant râles and thickened pleura over this area; sharpened breath sounds almost amphoric over upper lobe of right lung. Roentgenogram: hilar markings increased on both sides with considerable thickening along bronchial tree at the base of both lungs; several thick-walled cylindric bronchi at base of right lung close to hilar region; no definite circular bronchiectases; fields of upper lobes clear			.. ..
½ to 4 wk.	Cholecystectomy 2 years before admission	1/1/28	C				.. ..
10 da. to 2 wk.	Admitted with sudden pain in upper part of abdomen and vomiting; 12/3: perforated gastric ulcer found near pylorus; this was inverted; chronic duodenal ulcer 2 cm. in diameter; acute duodenal ulcer 8 mm. found at autopsy	12/24					+ +
5 wk.	Extensive focal pulmonary anthracosis with deposits from 2 to 3 mm. in diameter in all lobes	3/9	..				+ +
2 wk.	Gangrenous osteomyelitis of the jaw; Vincent's stomatitis; 2/25 and 26: acute cellulitis of the soft tissues of the jaw with hemorrhage from mouth	2/26	..				+ +
6 mo.	Chronic salpingitis and oophoritis; chronic appendicitis and periappendicitis; signs of splenic infarction 8/23; fecal fistula (abdominal sinus) with drainage continuing until just before discharge	9/28	I	6/15: resection of rib (local and general anesthesia); drainage and irrigation with surgical solution of chlorinated soda; 7/31: considerable foul-smelling discharge from sinus in chest; 8/7 to 8/18: purulent discharge from chest sinus			.. ..
5 wk.	Carcinoma of the larynx	4/28	I				.. ..
Several months	Carcinoma of the larynx with metastases to the regional nodes	7/3	I				.. ..
ver 4 yr.; acerbation t present	Mitral stenosis	5/18	I				.. ..
		8/13	I slightly	6/25/28: resection of ribs; 6/16, 20 and 21: thoracentesis			.. ..
		4/29	I	4/1/29: excision of bronchial (right) fistula (general anesthesia)			.. ..
		12/4 unimproved	..	11/15/29: Incision and drainage of region of old fistula (local anesthesia)			.. ..
		7/1	I somewhat	6/1/31: phrenicectomy (right); after leaving hospital patient was treated by Dr. S. Sogg for weakness, cough, chronic empyema, bronchial fistula; died suddenly 11/3; had fever shortly before death			.. ..
7 wk.		5/16	I slightly 5 days after admission (insufficient treatment)				.. ..
6 wk.		8/3	I	Maculopapular rash few hours after third injection of neoarsphenamine; 2/3/33: general condition good; some hoarseness, some cough, since leaving hospital; physical examination of chest normal; roentgen findings: considerable beaded peribronchial thickening at bases of both lungs			.. ..
7 wk.	Diabetes mellitus treated with insulin; 8/18: teeth extracted (local anesthesia)	9/13	I				.. ..
w months	General vascular syphilis; fever, convulsions, no cerebral lesion	11/14	..				+ +

pulmonary spirochetosis

sionally bloody

					then slightly irregular, not over 101 F., gradually falling after injection of arsphenamine to normal or subnormal	phenamine; 8/15: 0.3 Gm., 8/22 and 24: 0.2 Gm. sulpharsphenamine; 8/27 and 9/4: 0.4 Gm..		
	11/ 2 11/ 8	11,500 13,500	81 84	Myelocytes	Moderate; 100 to 102 F. for few weeks, then gradually less for 5 weeks with rise to 102.5 F.	9/25, 10/6: 0.45 Gm. neoarsphenamine; 10/16: 0.6 Gm.	Few months	
35 M. N. Male	White 41 4/13/28	+	..	..	4/14, roentgenogram: pneumonia with effusion in right base; 5/14: thickened pleura	.....	+	.....
	6/14/28	..	..	..	7/10, roentgenogram: encapsulated empyema	.....	Drainage of pus	.....
	3/29/29	..	..	..	.....	.....	Drainage of pus	.....
	11/12/29	..	..	..	11/14, roentgenogram: old resection of ninth, tenth and eleventh ribs	.....	Drainage of pus	.....
	5/20/31	..	..	..	.....	.....	Drainage of pus	.....
36 J. P. Male	White 62 5/11/28	..	..	+	5/12, roentgenogram: necrosis	.....	.....	.....
37 S. S. Female	White 42 7/3/28	..	..	+ Early	.....	7/11, roentgenogram: suggestive of cavity; 7/30: less signs	.....	.....
38 S. S. Male	White 40 8/3/28	..	..	+	8/4, roentgenogram: necrosis	.....	.....	.....
39 T. P. Male	White 42 9/18/28	..	..	+	At autopsy on 10/31: definite infiltration on roentgen examination of chest not found	.....	500 cc. of foul-smelling pus in right side of chest	No M-V gram-n bacilli
40 G. H. Male	White 27 11/12/28	..	+	..	11/14, roentgenogram: area of diminished density	.....	.....	.....
41 J. M. Male	White 38 11/18/28	..	..	+	Physical examination; no roentgen study	.....	.....	.....
42 A. Z. Male	White 68 1/13/29	..	..	+	.....	1/14, roentgenogram: cavity	.....	.....
43 I. E. Male	White 66 10/15/29	..	..	+	11/13, 12/3, roentgenogram: necrosis	.....	.....	.....
44 S. W. Female	White 42 12/15/29	+	..	..	12/16, roentgenogram: bronchiectatic cavity	.....	.....	.....
45 L. A. Female	White 49 8/4/30	..	..	+	.....	8/4, roentgenogram: diminished density and infiltration (lung abscess); spirochetosis (?)	.....	.....
46 M. S. Male	White 69 9/28/30	..	..	+	Cavity 2 cm. by 5 mm. found at necropsy; thin, brown, foul-smelling contents	Purulent bronchitis in lower lobe of both lungs with bronchopneumonia	.....	.....
47 H. A. Female	White 14 3/17/31	..	..	+	.....	4/13, roentgenogram: bronchopneumonia in upper lobe; 4/24: cavity and infiltration beginning 17 days post-operatively	.....	.....
48 V. M. Female	White 20 6/1/31	..	..	+	6/21 and 23, roentgenograms: cavity in upper lobe; 7/23: cavity could not be outlined with certainty	.....	.....	.....
49 L. G. Male	White 10 8/12/31	..	..	+	9/5, roentgenogram: small cavity	.....	8/13: large amount foul, green-black fluid	Fusifor bacilli; spiroch
50 A. T. Female	White 48 2/15/32	..	..	+	.....	Cavity (2 cm.); early stage of bronchopneumonia in all lobes, found at autopsy; M-V in direct smears of wall of cavity	.....	.....
51 P. S. Male	White 3 7/9/32	..	..	+	8/25, roentgenogram: areas of necrosis	.....	500 cc. gangrenous effusion	9/
52 W. G. Male	White 60 9/15/32	..	+	..	.....	No roentgen studies; 9/28: clinical diagnosis of bronchopneumonia and gangrene in lower lobe	.....	.....
53 W. H. Male	White 38 3/16/33	+	..	+	3/18, roentgenogram: numerous rounded areas of diminished density (cavitation) in upper lobe; 5/18: still slightly mottled; increased density in upper lobe, slight honeycombing suggesting bronchiectases	.....	4/21: localized empyema in upper lobe of right lung	4/
54 V. A. Female	White 25 3/17/33	..	+	..	4/5, roentgenogram: very slight cloudiness in lower hilus extending over base of lung field	.....	.....	.....
55 A. B. Male	White 53 4/20/33	+	..	..	.....	4/21/33, roentgenogram: dense cloudiness at base; 4/24: injection of iodized poppy-seed oil 40% revealed no bronchiectatic cavities	4/28: pus obtained on thoracentesis; 5/2: encapsulated empyema in left lung (1 oz. [29.5 cc.] pus expelled); smear showed small gram-negative bacilli	.....

* M-V means Miller-Vincent organisms.

Few months	General vascular syphilis; fever, convulsions, no cerebral lesion	11/14	..	..	..	..	..	..	..
		pulmonary spirochetosis		sionally bloody					
		+ Present admission exacerbation (?)		Thick, yellow occasionally blood-streaked	+ 4/26, 5/8, 9, 14	Teeth in good condition	4/14 4/29 5/18	15,750 25,400 22,000	8 7
					+ 6/15, 21: B. fusiformis and vibrios		6/14 7/18 8/ 1	19,200 14,550 14,200	
						Moderate number of M-V in oral smear	3/30	13,300	
				12/3: yellow mucopus, no M-Vs; 12/4: much blood, no M-V			11/13 11/30	10,600 6,200	
				6/8: mucopurulent		Teeth fair	5/20 5/31 6/12 7/ 1	19,800 18,400 14,600 11,600	
		+		Sputum beginning 6 or 7 weeks before admission; foul odor to breath	+ 5/12, 16	Gums and teeth in poor condition	5/12	13,800	7
			+ 6/21 and 23: local; teeth extracted	Foul-smelling, beginning 6 days before admission	+ 7/5, 6, 11, 12, 13, 14, 17, 18 and 20	Marked gingivitis	7/ 3 7/ 7 7/25	11,200 8,800 9,000	7
		+		Foul-smelling, beginning 1 week before admission	+ 8/4: fusiform bacilli and vibrios, no spirochetes; 8/11, 12, 15 and 18: spirochetes	Gums and teeth in poor condition, tongue sore	8/ 3	21,950	7
elling of	No M-V (small gram-negative bacilli)	+		Small amount of foul-smelling, beginning 3 weeks before admission	In smears of lung post mortem	9/25: acute gingivitis, M-V	11/ 2 11/ 8 11/14	11,500 13,500 8,000	8 8 3
		+		Blood-tinged on admission; 11/14: bloody	+ 11/13	Teeth in fair condition	11/13	15,000	8
		+		History of expectoration of large amount of purulent, foul-smelling sputum; 11/21: sometimes bloody	+ 11/21	Teeth bad; gingivitis	11/18	11,050	8
				1/13: foul-smelling, large quantity	+ 1/14 and 16	Teeth and gums in poor condition	1/13	12,200	8
		+		10/19: foul odor; 10/21: brownish-yellow	+ 10/17	Teeth and gums in bad condition	10/15 10/24	9,000 14,400	8
		+		Blood-tinged, purulent before and after admission; foul odor occasionally	+ 12/16, 17 and 19	Mouth in fair condition; 12/17, roentgenogram: abscess of one tooth	12/15	10,900	6
			+ General: tonsillectomy 3 weeks before admission	Large amount of green, foul-smelling, before admission	+ 8/4, 9 and 13	Teeth in fair condition	8/ 5	14,000	8
			+? Local: suprapubic cystotomy		Fusiform bacilli in smear of teeth post mortem	Dental caries and gingivitis; foul odor on admission; gangrenous stomatitis at autopsy	.....	.....	
			+ 3/27: general: tonsillectomy	Greenish-yellow after tonsillectomy, breath foul	+ 4/23, 24 and 29: fusiform bacilli; 4/25: other M-V 4/26, 28, 5/5: few	Teeth in good condition, tonsils large	3/17	11,400	5
			+ 6/3: general: delivery and repair following second pregnancy	Very foul, beginning 6/23	+ 6/29: moderate number of fusiform bacilli; 7/3: moderate number, few spirochetes; 7/5: many fusiform bacilli, moderate number of spirochetes	No record	6/22 7/ 4 7/24	10,800 12,600 8,550	7 7
t fluid	Fusiform bacilli; no spirochetes	+		Foul-smelling; 8/13: green-brown	+ 8/12 and 13	Few decayed teeth; breath foul; 8/5: M-V in gingival smear	8/12 8/24 9/22	30,050 17,150 15,000	7 5
		+ After lye poisoning		0	0	Areas of necrosis in buccal mucosa on admission; gangrenous sloughs; dental caries and gingivitis at autopsy	2/16	14,800	6
s	+ 9/13	+		8/17: purulent	+ 7/13 and 25: few B. fusiformis on swab; 8/31: moderate number; 9/5: many fusiform bacilli	No oral lesion; 9/9: fusiform bacilli and few spirochetes	7/ 9 7/23 8/ 1 8/11 8/23 9/15	22,000 39,000 28,000 28,300 27,900 12,200	8 8 3
			+ 9/19: general: prostatectomy	9/25: mucopurulent; 9/26: purulent, blood-tinged; 9/27: greenish, foul (?)	+ 9/27	No lesion; fusiform bacilli in smear of throat	9/16	7,350	
r	+ 4/21	+		4/10: watery, purulent, very foul odor; 5/17: greenish-white mucopurulent, with few white balls (no odor); bloody at times before admission as well as foul smelling	+ 3/25, 4/10, 5/17	Teeth in bad condition, pyorrhea	3/16 3/27	6,300 7,200	6
		+		No record	+ 3/19	Teeth and gums in fair condition; pharynx injected	3/17 3/18	13,850 14,200	8
d on : yema [29.5 cc.] ear showed ive		+		Mucopurulent, occasionally blood-streaked before admission; mucopurulent in hospital, no odor	+ 4/21, 24 and 25	Marked oral sepsis	4/20	9,200	6

* M-V means Miller-Vincent organisms.

...	6/ 9	8,200	..	..	..	Slight elevation for a few days after removal (local anesthesia) of cervical nodes, not over 101 F., then normal	6/20 and 25: 0.6 Gm. neoarsphenamine	Several months	arcinom ses to
n-	4/14 4/29 5/18	15,750 25,400 22,000	82 78	..	..	103.5 F. on admission, 104.5 F. 2 days later, then fell to about 100 or 101 F. for few weeks, then somewhat less, later slightly irregular, 99 F. on discharge	4/30, 5/11 and 14: 0.6 Gm. neoarsphenamine; 5/17: 0.9 Gm.	Over 4 yr.; exacerbation at present	Mitral s
...	6/14 7/18 8/ 1	19,200 14,550 14,200	..	..	..	About 100 F. for one week but intermittent, somewhat lower beginning a few days after thoracostomy; slightly irregular with occasional rise over 100 F.; 97 F. at discharge	0	.....	.....
r near	3/30	13,300	..	..	..	98.6 F. on admission; elevated for 6 days postoperatively, falling from 103 F.; slight thereafter; 97 F. on discharge	0	.....	.....
...	11/13 11/30	10,600 6,200	..	..	..	99.6 F. on admission; elevated for about 1 week beginning 3 days after incision, falling steadily from 103.5 F. to normal	0	.....	.....
	5/20 5/31 6/12 7/ 1	19,800 18,400 14,600 11,600	..	..	..	102 F. on admission; irregular, usually slight, occasionally to 101 or 102 F.; 98 F. on discharge	0	.....	.....
in	5/12	13,800	76	..	..	99.5 to 100 F.	5/12 and 15: 0.9 Gm. neoarsphenamine	7 wk.	.....
is	7/ 3 7/ 7 7/25	11,200 8,800 9,000	.. 79	..	..	101 F. on admission; fell to normal in 24 hours after injection of arsphenamine; slight elevation for few days; then 100 to 103 F. for several days, then 100 F. or less. Normal about 10 days before discharge	7/3, 6 and 10: 0.6 Gm. neoarsphenamine	6 wk.	.....
in	8/ 3	21,950	75	..	..	100.8 F. on admission; normal several days, then slightly irregular, not over 101 F., gradually falling after injection of arsphenamine to normal or subnormal	8/4, 6, 9 and 12: 0.6 Gm. neoarsphenamine; 8/15: 0.4 Gm.; 8/22 and 24: 0.2 Gm. sulpharsphenamine; 8/27 and 9/4: 0.4 Gm..	7 wk.	Diabetes 8/18: teet
	11/ 2 11/ 8 11/14	11,500 13,500 8,000	81 84 31	Myelocytes, 15		Moderate; 100 to 102 F. for few weeks, then gradually less for 5 weeks with rise to 103.5 F. beginning 5 days before death	9/25, 10/6: 0.45 Gm. neoarsphenamine; 10/16: 0.6 Gm.	Few months	General vulsions,
n-	11/13	15,000	81	..	..	101 F. on admission, then less (to 99.5 F.) for several days, then steadily increasing to 104 F. (11/20) with drop to 100.5 F. on 11/22	11/17: 1 injection of neoarsphenamine	10 wk.	Bacterial septicemi
	11/18	11,050	82	..	..	Irregular, reaching 102 F. day before death	0	4 to 9 mo.	Partial p
in	1/13	12,200	88	..	..	100 to 102 F. for 1 week, then 98 to 100.5 F.	1/14: 0.45 Gm. neoarsphenamine; 1/16 and 19: 0.6 Gm.	3½ wk.	Diabetes
in	10/15 10/24	9,000 14,400	84	..	..	100 to 101 F. for 1 week, then less; at times subnormal	10/19, 21, 24 and 29, 11/1, 7 and 9: 0.45 Gm. neoarsphenamine; 11/6: 0.3 Gm.	2 mo.	Diabetes trose and
n- ent- ess	12/15	10,900	64	..	..	98 F. on admission; slightly irregular; occasionally to 100.5 F. (98 F. on discharge) usually about 99 F.	0	1 yr.	Postural
-	8/ 5	14,000	84	..	..	98.4 F. on admission, rising to 102.5 F. in few days; then about 100 to 100.5 F. throughout course, occasionally higher. 103.5 F. at death	0	2 mo.	Diabetes
d on; na-	.....	.....	..	..	..	103.5 F. on admission; fell to normal in few days, then rose to 102 F. before death	0	8 da.	Prostatic gangreno cystotomy and intes exudate
on-	3/17	11,400	59	..	..	100.5 F. on admission, irregular, slight; elevation to 101.5 F. 4 days after tonsillectomy, then about 100 to 101 F., occasionally to 103 F. for several weeks, gradually subsiding. About normal for a few weeks before discharge	4/14, 21 and 24, 5/13: 0.45 Gm. neoarsphenamine; 4/27 and 30, 5/8: 0.2 Gm. sulpharsphenamine intramuscularly	6 wk.	Acute rh ciency; f admission
	6/22 7/ 4 7/24	10,800 12,600 8,550	73 72	..	..	98.2 F. on admission, rising sharply to 102 F. on 6/17 (14 days postoperatively), then 101 to 102 F. for few weeks, falling to normal on 7/8, remaining about normal with few elevations until discharge. 97.6 F. on discharge	6/22, 7/18: 0.3 Gm. neoarsphenamine; 6/24, 27 and 29, 7/2, 7 and 21: 0.6 Gm.	5½ wk.	.....
th; :	8/12 8/24 9/22	30,050 17,150 15,000	78 58	Lymphocytes 40		103 F. on admission; average about 102 F. for about 10 days; once to 105 F.; fell gradually to 100 F. on 8/28; then greater part of time about 100 F. until discharge (99.5 F.)	8/13, 15 and 17: 0.2 Gm. neoarsphenamine; 8/20, 24 and 27, 9/1: 0.3 Gm.	10 wk.	9/5, roent
s a an- . d	2/16	14,800	64	..	..	100 F. on admission; generally 100 to 102 F. for few weeks, then about 100 F. 1 week, rising to 103 F. before death	0	3 wk.	Lye pois itis; gast
	7/ 9 7/23 8/ 1 8/11 8/23 9/15	22,000 39,000 28,000 28,300 27,900 12,200	87 85 39	.. 52	..	Remittent; 103 F. on admission; 104.5 F. on 7/29; 100 F. or less beginning 9/18	9/2: 0.2 Gm. neoarsphenamine; 9/6, 9 and 12: 0.15 Gm.	5 mo.	8/19, roe 7/17, 8/15 blood tra
orm	9/16	7,350	..	..	..	Remittent, then intermittent, beginning 9/19 p. m., after operation; 105.3 F. on 9/22; 102 F. at death	0	9 da. (postoperatively)	Nodular syphilis; mg., 9/21 86 mg., 9 9/28, 115 m
n- a	3/16 3/27	6,300 7,200	68	..	..	102 F. on admission, falling to normal in several days; slightly elevated for 3 weeks (under 100 F.), then 100 to 102 F. for few weeks with fall to normal for several weeks	3/30, 4/2, 6 and 9: 0.45 Gm. neoarsphenamine; 4/22, 26 and 30, 5/18: 0.6 Gm.	4½ mo.	.....
in	3/17 3/18	13,850 14,200	.. 81	..	..	102.2 F. on admission, falling to 100 F. in few days, remaining for 10 days then gradually to normal just before discharge	4/1: 0.3 Gm. neoarsphenamine; 4/5: 0.45 Gm.	3 wk.	Ovarian
is	4/20	9,200	68	..	..	101 F. on admission; irregular throughout stay; 100 to 101 F., occasionally higher; 99 for 1 week until 10 days before discharge, after which intermittent and somewhat higher	4/26: 0.45 Gm. neoarsphenamine	6 mo.	Osteo-art spine; ch fistula in

...rcinoma of the larynx with metastases to the regional nodes	7/3	I	.....	..	..
Mitral stenosis	5/18	I	.....	..	..
.....	8/13	I slightly	6/25/28: resection of ribs; 6/16, 20 and 21: thoracentesis.....	..	..
.....	4/29	I	4/1/29: excision of bronchial (right) fistula (general anesthesia).....	..	..
.....	12/4 unimproved	..	11/15/29: Incision and drainage of region of old fistula (local anesthesia).....	..	..
.....	7/1	I somewhat	6/1/31: phrenicectomy (right); after leaving hospital patient was treated by Dr. S. Sogg for weakness, cough, chronic empyema, bronchial fistula; died suddenly 11/3; had fever shortly before death	..	..
.....	5/16 5 days after admission (insufficient treatment)	I slightly	.....	..	..
.....	8/3	I	Maculopapular rash few hours after third injection of neoarsphenamine; 2/3/33: general condition good; some hoarseness, some cough, since leaving hospital; physical examination of chest normal; roentgen findings: considerable beaded peribronchial thickening at bases of both lungs	..	..
Diabetes mellitus treated with insulin; 8/18: teeth extracted (local anesthesia)	9/13	I	.....	..	..
General vascular syphilis; fever, convulsions, no cerebral lesion	11/14	..	.....	+	+
Bacterial endocarditis: pneumococcic septicemia	11/22 unimproved	..	.....	..	..
Partial pneumothorax	11/21	..	11/19: abscess in wall of right side of chest; foul-smelling (no thoracentesis previously); 11/19: resection of ribs; no pus	+ 3 days after admission	0
Diabetes mellitus treated with insulin	1/30	..	Pulmonary disturbance a week after extraction of tooth (anesthesia given ?)...	+	0
Diabetes mellitus treated with dextrose and insulin; insulin shock twice	12/8	..	11/23: right phrenicectomy (local anesthesia).....	+	0
Postural drainage	12/29	I	.....	..	..
Diabetes mellitus treated with insulin	9/13	..	9/11: phrenicectomy	+	0
Prostatic hypertrophy with retention; gangrenous cellulitis in suprapubic cystotomy wound; fusiform bacilli and intestinal organisms in peritoneal exudate	10/6	..	.....	+	+
Acute rheumatic fever; mitral insufficiency; fever and pain in joints on admission	5/25	I well	.....	..	..
.....	7/26	C	11/3/31: admitted to Warrensville Sanitarium with evidence of large cavity in right lung; several examinations of sputum failed to reveal tubercle bacilli; no sputum obtained after 11/9/31. Repeated roentgenograms of chest showed cavity progressively smaller; 2/27/32: cavity still visible much smaller than previously; 4/6: cavity no longer visible; 11/6: patient discharged improved; condition arrested; since then has been working daily in the sewing room of the institution	..	..
9/5, roentgenogram: pneumothorax...	10/9	C	8/13/31: resection of right ribs; irrigation with surgical solution of chlorinated soda; 2/3/33: perfectly well since discharge; wound well healed; signs of thickened pleura in right side of chest at site of operation; roentgen findings: moderate peribronchial thickening throughout lung fields	..	..
Lye poisoning; necrotizing esophagitis; gastritis	3/8	..	.....	+	+
8/19, roentgenogram: pneumothorax; 7/17, 8/15: bronchoscopy; 9/2 and 15: blood transfusion	11/9	I	7/25/32, 9/10: thoracentesis; no fluid obtained; 9/13: resection of ribs; 9/18: icterus, enlarged liver following 4 injections of neoarsphenamine; 1/20/33: well and happy, no complaint		
Nodular hyperplasia, prostatitis; syphilis; nonprotein nitrogen: 9/16, 33 mg., 9/21, 42 mg., 9/23, 83 mg., 9/24, 86 mg., 9/26, 111 mg., 9/27, 143 mg., 9/28, 115 mg.	9/29/32	..	.....	+	0
.....	5/2 ..	I	First admission 1/17/33 to 2/3 with abscess following pneumonia; ordinary organisms in washed sputum; 1/21: no spirochetes, a few fusiform bacilli; 4/14: resection of ribs	..	..
Ovarian cyst	4/5	I	.....	..	..
Osteo-arthritis of lower portion of spine; chronic empyema with bronchial fistula in the left lung	6/10	I	4/28 and 30: thoracentesis; 5/2: resection of ribs.....	..	..

Although pulmonary gangrene almost invariably results from the aspiration of oral spirochetes, fusiform bacilli and vibrios from the mouth, it has been reported [17] following embolism from putrid puerperal infections, gangrenous decubitus ulcers and degenerating tumors of the intestines and female genitals. The form and situation of early pulmonary lesions of this type are much like those following embolism of pyogenic organisms.

TABLE 4.—*Results of Tests for Syphilis in Cases of Infection with the Miller-Vincent Organism*

	Reaction	Wassermann Test	Diagnostic Slide Test
In cases with no evidence of syphilis.....	Negative	14	7
	Positive	0	0
	Doubtful	2 1 anticomplementary	1
In cases with evidence of syphilis.....	Positive	2	1
	Negative	2	2

SUMMARY

Table 2 summarizes the ninety cases of pulmonary abscess and of pulmonary gangrene and other types of Miller-Vincent's infection of the lung observed at Mount Sinai Hospital in the past ten years.

The fifty-five cases of Miller-Vincent's pulmonary infection in this series are described briefly in table 3.

Table 4 summarizes the results of tests for syphilis. It shows that in cases of infection with the Miller-Vincent organisms the blood did not give positive reactions in tests for syphilis unless this disease also was present.

17. Lauche, A.: Die Entzündungen der Lunge und des Brustfelles, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 3, pt. 1, p. 862.

TREATMENT OF CARDIOVASCULAR SYPHILIS

A STUDY OF THE DURATION OF LIFE IN EIGHTY TREATED AND UNTREATED PATIENTS WITH AORTIC ANEURYSM AND AORTIC REGURGITATION

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In 1930 Moore and Danglade [1a] published an article on the treatment of cardiovascular syphilis. They together with Reisinger [1b] followed this in 1932 with a similar article. These articles were particularly valuable because, with the use of various self-explanatory charts, they detailed the facts which many older clinicians had failed to record in the analysis of the effects of specific treatment on cardiovascular syphilis.

Inasmuch as there have been published only five other papers in which similar data have been recorded,[2] it seemed to the San Francisco Heart Committee and to me that a compilation of statistics made from the records of the various San Francisco hospitals according to the excellent chart forms originated by Moore and his co-workers would be an interesting contribution. The following statistics have been assembled with the courteous cooperation of the Medical Department of the Stanford University Hospitals, the University of California Hospital and the San Francisco County Hospital.

On this basis, the patients are divided into the following four treatment groups:

Group 1.—Those who received no treatment or very little (one or two injections of arsphenamine or three or four injections of bismuth or inunctions of mercury) for less than a month.

These statistics were assembled and the charts prepared with the help of Miss Rosemary T. Kobes, R.N., Cardiac Field Worker, San Francisco Heart Committee.

1. (*a*) Moore, J. E., and Danglade, J. H.: Treatment of Cardiovascular Syphilis: A Study of the Duration of Life in One Hundred and Forty-One Treated and Untreated Patients with Aortic Regurgitation and Aortic Aneurysm, Am. Heart J. **6**:148 (Oct.) 1930. (*b*) Moore, J. E.; Danglade, J. H., and Reisinger, J. C.: Treatment of Cardiovascular Syphilis: Results Obtained in Fifty-Three Patients with Aortic Aneurysm and in One Hundred and Twelve with Aortic Regurgitation, Arch. Int. Med. **49**:879 (June) 1932.

2. Reid, M. D.: Prognosis of Specific Aortitis, J. A. M. A. **73**:1832 (Dec. 13) 1919. Cotton, F. F.: Cardio-Aortic Syphilis and Its Treatment, Brit. M. J. **1**:855, 1926. Conybeare, J. J.: Treatment of Aortic Aneurysm by Anti-Syphilitic Remedies, Guy's Hosp. Rep. **74**:163, 1924. Herrmann, G., and Jamison, C.: Treatment of Cardiovascular Syphilis with Especial Reference to Aortic Regurgitation with Congestive Heart Failure, Am. J. Syph. & Neurol. **15**:1, 1932. Barnett, C. W.: Effect of Specific Treatment in the Prognosis of Syphilis of the Cardiovascular System, Arch. Dermat. & Syph. **28**:1 (July) 1933.

Group 2.—Those who were treated for a period of from six to twelve weeks (the equivalent of one course of arsenical treatment or one long course of treatment with a heavy metal).

Group 3.—Those treated for a period of from three to twelve months (roughly the equivalent of a long course of treatment with an arsenical plus a long course of treatment with a heavy metal).

Group 4.—Those treated for more than a year.

I have investigated 750 history charts bearing the diagnosis of cardiovascular syphilis. Of this number, 200 bore the definite diagnosis

TABLE 1.—*Patients with Aneurysm: Treatment, Group 1*

Patient	Age	Living or Dead	Duration of Life (Months) Until Death or Last Observation Measuring from: Onset of Symptoms	Duration of Life (Months) Until Death or Last Observation Measuring from: Start of Treatment	Cardiac Failure: Before Treatment*	Cardiac Failure: After Treatment	Duration of Symptoms Before Treatment, Mos.	Aortic Regurgitation Also present
1	57	D	2	1	A 1	.....	1	....
2	63	D	5	2	C 1, A 1	.....	3	Yes
3	40	D	6	2	C 2	.....	4	Yes
4	62	D	6	3	C 2	.....	3	....
5	50	D	7	2	C 1, A 1	.....	5	Yes
6	37	D	8	..	C 2	.....	8	Yes
7	57	D	8	4½	C 1, A 1	.....	3½	Yes
8	48	D	9	3	A 1	.....	6	....
9	51	D	11	1	C 2, A 1	.....	10	....
10	60	D	11	4	C 2	.....	7	....
11	60	D	12	3	C 2, A 1	.....	9	....
12	46	D	12	1	C 1, A 1	.....	11	....
13	59	D	13	1	C 1	.....	12	....
14	66	D	14	..	C 2, A 1	.....	14	....
15	[illegible]	D	16	15	C 2	.....	1	....
16	55	D	17	10	C 2, A 1	.....	7	Yes
17	49	D	17	15	A 1	.....	2	Yes
18	58	D	19	4	C 2	.....	15	Yes
19	61	D	29	11	C 1, A 2	.....	18	....
20	58	D	34	21	C 1, A 1	.....	13	....
21	75	D	36½	½	C 1, A 1	.....	36	....
22	49	D	38	19	C 1	.....	19	....
23	52	D	39	8	C 2, A 1	.....	31	Yes
24	47	D	60	5	C 3, A 2	.....	55	Yes
25	57	D	64	4	C 2, A 1	.....	60	....
26	50	D	109	1	C 1	.....	108	....
27	41	D	5	13	.....	C 2, A 1	0	....
28	45	L	106	10	C 1	.....	96	Yes

* In this and subsequent tables A means anginal failure and C congestive failure; 1, 2 and 3 are used to represent the degrees of severity of symptoms.

of either aneurysm or aortic regurgitation, and of these patients with aneurysm or aortic regurgitation 92 were known to be either dead or in active attendance at the clinics of the three institutions at the time these statistics were compiled.

Forty-three of the patients had aneurysm; 4 of these were living and 39 were dead. Forty-nine patients had aortic regurgitation, 14 of these were living and 35 were dead. Twelve patients from these two groups (11 in group 1 and 1 in group 2) had both these conditions. I had, therefore, a total of 80 patients from whose histories I finally compiled the accompanying tables.

Since none of these patients had at any time been under my observation, the data herein presented are those transcribed from their history charts. There was nothing in their histories to indicate that any of them had received antisyphilitic treatment for their cardiovascular lesions before admission to the clinics.

TABLE 2.—*Patients with Aneurysm: Treatment, Groups 2, 3 and 4*

Patient	Age	Living or Dead	Duration of Life (Months) Until Death or Last Observation Measuring from: Onset of Symptoms	Duration of Life (Months) Until Death or Last Observation Measuring from: Start of Treatment	Cardiac Failure: Before Treatment	Cardiac Failure: After Treatment	Duration of Symptoms Before Treatment, Mos.	Aortic Regurgitation Also Present
				Group 2				
1	45	D	8	7	C 2	.....	1	N..
2	61	D	19	18	C 2	.....	1	....
3	50	L	27	17	A 1	.....	10	....
4	40	D	41	29	C 1	.....	12	....
5	51	D	51	29	C 2, A 1	.....	22	....
6	65	D	79	43	C 2, A 2	.....	36	Yes
				Group 3				
1	47	L	55	54	C 1, A 1	.....	1	....
2	57	D	21	18	C 2	.....	3	....
3	47	L	15	7	Pressure	.....	8	....
4	55	D	52	28	C 2, A 2	.....	24	....
5	48	L	65	10	Pressure	.....	55	....
				Group 4				
1	37	D	24	144	.....	C 2	None	....
2	50	D	54	372	.....	C 2	None	....
3	52	D	44	42	C 1	.....	2	....
4	46	D	41	36	C 2, A 1	.....	5	....

TABLE 3.—*Effect of Treatment on Prolongation of Life in Patients with Aneurysm of the Aorta (Forty-Three Cases; Four Living, Thirty-Nine Dead)*

Treatment Group	Average Age, Yrs.	Patients in Group	Patients Living	Patients Dead	Average Duration of Symptoms Before Treatment, Mos.	Average Duration of Life (Months) Until Death or Last Observation Dating from: Onset of Symptoms	Average Duration of Life (Months) Until Death or Last Observation Dating from: Start of Treatment
Group 1	54.4	28	1	27	19.9	25.4	5.8
Group 2	52	6	1	5	13.7	37.5	23.8
Group 3	50.8	5	2	3	18.2	41.6	23.5
Group 4	46.2	4	0	4	1.8	40.7	148.5

It is interesting to note that practically every one of these patients complained of some type and degree of cardiac failure before antisyphilitic treatment was instituted. In the columns headed "Cardiac Failure" I used the letter C and A to designate congestive and anginal failure, respectively, and the grades 1, 2 and 3 to denote the severity of the symptoms.

TABLE 4.—*Patients with Aortic Regurgitation: Treatment, Group 1*

Patient	Age	Living or Dead	Duration of Life (Months) Until Death or Last Observation Measuring from		Cardiac Failure		Duration of Symptoms Before Treatment, Mos.	Aneurysm Also Present
			Onset of Symptoms	Start of Treatment	Before Treatment	After Treatment		
1	36	D	3	2	C 3	.....	1	....
2	56	D	3	2	C 1	.....	1	....
3	38	D	3	1	C 2, A 1	.....	2	....
4	62	D	3	1	C 2, A 1	.....	2	....
5	50	D	4	1	C 2	.....	3	....
6	63	D	5	2	C 2, A 1	.....	3	Yes
7	58	D	6	2	C 2	.....	4	....
8	60	D	6	None	C 2	.....	6	....
9	40	D	6	2	C 2	.....	4	Yes
10	50	D	7	2	C 1, A 1	.....	5	Yes
11	57	D	8	4	C 2, A 1	.....	4	Yes
12	37	D	8	None	C 2	.....	8	Yes
13	40	D	14	2	C 2	.....	12	....
14	49	D	15	None	C 2	.....	15	....
15	49	D	16	14	A 1	.....	2	Yes
16	55	D	17	10	C 2, A 1	.....	7	Yes
17	51	L	18	13	C 1	.....	5	....
18	58	D	19	4	C 2	.....	15	Yes
19	48	L	21	192	.....	C 3	None	....
20	56	D	25	1	C 1	.....	24	....
21	43	D	24	None	C 2	.....	24	....
22	68	D	26	24	C 2	.....	2	....
23	52	D	39	8	C 2, A 1	.....	31	Yes
24	47	D	60	5	C 3, A 2	.....	55	Yes
25	39	D	68	8	C 2	.....	60	....
26	45	L	106	10	C 1	.....	96	Yes
27	56	L	119	111	C 1, A 1	.....	8	....

TABLE 5.—*Patients with Aortic Regurgitation: Treatment, Groups 2, 3 and 4*

Patient	Age	Living or Dead	Duration of Life (Months) Until Death or Last Observation Measuring from		Cardiac Failure		Duration of Symptoms Before Treatment, Mos.	Aneurysm Also Present
			Onset of Symptoms	Start of Treatment	Before Treatment	After Treatment		
Group 2								
1	32	D	4	3	C 2, A 2	.....	1	....
2	47	D	8	6	C 2	.....	2	....
3	58	D	7	4	C 2	.....	3	....
4	59	D	8	4	C 1	.....	4	....
5	32	D	27	3	C 1	.....	24	....
6	65	D	79	43	C 2, A 2	.....	36	Yes
Group 3								
1	50	D	8	20	.....	C 2, A 1	None	....
2	65	D	44	43	C 2	.....	1	....
3	47	D	27	22	C 2, A 1	.....	5	....
4	61	D	17	8	C 1, A 1	.....	9	....
Group 4								
1	62	L	33	141	.....	C 1	None	....
2	53	L	29	336	.....	C 1	None	....
3	55	L	48	101	.....	C 1	None	....
4	48	L	48	131	.....	C 1	None	....
5	38	L	54	180	.....	A 1	None	....
6	64	D	50	49	C 2, A 1	.....	1	....
7	50	L	74	73	C 1	.....	1	....
8	57	L	124	120	C 2	.....	4	....
9	37	D	47	32	C 2, A 1	.....	15	....
10	36	L	76	31	C 1	.....	45	....
11	55	L	82	22	C 1	.....	60	....
12	59	L	156	62	C 1	.....	94	....

TABLE 6.—*Effect of Treatment on Prolongation of Life in Patients with Aortic Regurgitation (Forty-Nine Cases; Fourteen Living, Thirty-Five Dead)*

Treatment Group	Average Age, Yrs.	Patients in Group	Patients Living	Patients Dead	Average Duration of Symptoms Before Treatment, Mos.	Average Duration of Life (Months) Until Death or Last Observation Dating from	
						Onset of Symptoms	Start of Treatment
Group 1	50.5	27	4	23	14.8	24	15.6
Group 2	48.8	6	0	6	11.7	22	10.5
Group 3	55.8	4	0	4	3.8	24	23.2
Group 4	51.1	12	10	2	18.3	69.6	106.5

TABLE 7.—*Effect of Treatment on Prolongation of Life in Whole Group of Patients with Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation; Eighty Cases; Seventeen Living, Sixty-Three Dead)*

Treatment Group	Average Age, Yrs.	Patients in Group	Patients Living	Patients Dead	Average Duration of Symptoms Before Treatment, Mos.	Average Duration of Life (Months) Until Death or Last Observation Dating from	
						Onset of Symptoms	Start of Treatment
Group 1	53	44	4	40	16.5	24.3	11.9
Group 2	49	11	1	10	10.5	25.3	14.8
Group 3	53	9	2	7	11.8	33.7	23.3
Group 4	49.9	16	10	6	14.2	62.4	117.0

TABLE 8.—*Symptomatic Relief Resulting from Antisyphilitic Treatment in Cardiovascular Syphilis*

Treatment Group	Patients with Aneurysm			Patients with Aortic Regurgitation		
	Total Number	No. Who Obtained Symptomatic Relief	No. Who Obtained No Relief	Total Number	No. Who Obtained Symptomatic Relief	No. Who Obtained No Relief
Group 1	28	1	27	27	3	24
Group 2	6	0	6	6	1	5
Group 3	5	3	2	4	3	1
Group 4	4	2	2	12	6	6

TABLE 9.—*Influence of Treatment on Ability to Work in Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Treatment Group	Patients with Data Available	A Number Unable to Work Before or After Treatment	B Number Unable to Work Before, but Able After Treatment	C Number Able to Work Before but Unable After Treatment	D Number Able to Work Before and After Treatment
Group 1	40	32	2	2	4
Group 2	10	7	1	..	2
Group 3	9	3	3	..	3
Group 4	13	1	2	1	9

Twenty-eight patients with aneurysm listed in table 1 had little or no antisyphilitic treatment, and therefore the information given in the column headed "Duration of Life Until Death or Last Observation, Measuring from Onset of Symptoms" represents the average life expectancy for such patients. The duration of symptoms before treatment would have practically no bearing on the outcome for this group. It may be significant that of this group, 11 patients or 39 per cent lived less than twelve months (an average of seven months) after the onset of symptoms, and 17 (61 per cent) lived from twelve to one hundred and nine months (an average of thirty-seven months).

It is to be regretted that table 2, which represents groups 2, 3 and 4 treated for aneurysms, does not list as many patients for each group as were listed for group 1. On the basis of the few cases recorded, however, it seems that antisyphilitic treatment in the case of syphilitic aneurysm is responsible for prolonging life for from twelve to sixteen months on the average (table 3).

In presenting the cases of aortic regurgitation table 4 represents 27 cases falling into group 1, and leads one to the same conclusion as table 1, representing the 28 cases of aneurysm falling into treatment group 1. Twelve of these patients or 44 per cent lived less than twelve months (an average of five months) after the onset of symptoms, and 15 (56 per cent) lived from twelve to one hundred and nineteen months (an average of thirty-nine months).

Again it seems that the lives of the few patients falling especially into group 4 were definitely prolonged by the use of antisyphilitic treatment (table 6).

COMMENT

Moore [1] has so completely covered the field of comment and deduction on similar charts that I have made no attempt to do other than offer these additional statistics in the hope that their inclusion may be of some value in ultimately arriving at a large enough total of similarly studied groups to make the findings conclusive.

RELATION OF ASTHMA TO SINUSITIS

WITH SPECIAL REFERENCE TO THE RESULTS FROM SURGICAL TREATMENT

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From the many aspects that present themselves we have chosen to discuss in this paper the importance of disease of the sinuses in asthma and the evidence that infective asthma is an allergic reaction to bacteria or their products and that disease of the sinuses is usually the primary focus of infection; further, we present our data showing the effect of surgical intervention on the sinuses in asthma.

Wherever pathologic condition of the nasal passages is mentioned in connection with our cases of asthma, we refer to disease of the sinuses; as far as the literature is concerned, however, vasomotor changes, septal deviations and simple turbinal hypertrophies are included, and there is little or no attempt to differentiate the histologic type of disease of the sinuses, that is, the suppurative or the hyperplastic. In all our cases of asthma the membrane of the sinuses has been of the true hyperplastic type.

In a former paper [1] we concluded that the hyperplastic membrane is primarily infective and represents a special reaction to bacteria determined by the allergic constitution of the person so infected; in other words, the thickening of the membranes is not a reaction to inhaled substances or to foods. This position is not universally conceded but was fully discussed in our former paper.

The recognition of the importance of disease of the sinuses in thoracic conditions is, oddly enough, of recent date. Bronchiectasis was described by Laennec [2] in 1819, and pathologic conditions of the nasal

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1. Grove, R. C., and Cooke, R. A.: Etiology and Nature of Chronic Hyperplastic Sinusitis, Arch. Otolaryng. **18**:622 (Nov.) 1933.

2. Laennec, R. T. H.: Traité de l'auscultation médicale et des maladies des poumons et du coeur, Paris, Brosson and J. S. Chaude, 1819.

passages have been recognized almost as long, but it was not until 1916 that the importance of the association of the two lesions was noted by Sergent.[3] Two years before, however, Thompson[4] had shown that the amount of secretion in bronchorrhea was influenced by treatment of the sinuses. Since that time there has grown up an enormous number of reports in the literature regarding this association of chronic disease of the sinuses with chronic nontuberculous infections of the chest.

Although this association of nasal and thoracic infection is established, the causal relationship is not, and some authors regard these conditions as concomitant manifestations of the same infection. The weight of opinion, however, is that disease of the sinuses is primary to chronic nontuberculous infections of the chest. This conclusion is based largely on the fact that relief from certain thoracic symptoms follows proper nasal therapy and on the explanation afforded by Mullin's[5] work in 1919 on lymphatic drainage of the nasal sinuses. He showed that although there is no direct lymphatic connection between the nasal sinus and the glands of the hilus or the lungs, foreign material and bacteria were carried from the sinuses by the lymphatic glands to the duct, to the superior vena cava, to the right side of the heart and thence to the lungs. The bronchial and mediastinal glands were involved in all cases, and supposedly they are secondarily involved by lymphatic absorption from the lungs.

According to Adam,[6] it was Herck who, in 1844, first recognized the importance of a nasal factor in asthma. Voltolini[7] in 1872 recorded 11 cases of asthma in which relief followed nasal polypectomy.

Among the more recent reports is that of Adam,[6] who found nasal lesions in 68 per cent of 850 cases, but from the context it is not clear whether he included septal deviations and vasomotor rhinitis.

Rackemann and Tobey[8] are variously quoted as having found involvement of the sinuses in from 44 to 65 per cent of 1,074 cases of asthma. Grant[9] gave his figures as 63 per cent in 107 cases.

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3. Sergent, Emile: Histoire suggestive de quelques faux tuberculeux. Diagnostic differentiel de la tuberculose pulmonaire et des affections des voies respiratoires supérieures, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1424, 1916.

4. Thompson, St. Clair: Some of the Symptoms and Complications of Sinusitis, Practitioner **92**:745, 1914.

5. Mullin, W. V.: The Lymph Drainage of the Accessory Nasal Sinuses, Tr. Am. Laryng., Rhin. & Otol. Soc., 1919, p. 23.

6. Adam, James: Asthma, ed. 2, St. Louis, C. V. Mosby Company, 1926, p. 97.

7. Voltolini, R.: Die Anwendung der Galvanokaustic, ed. 2, Vienna, Wilhelm Braumüller, 1871, pp. 246 and 312.

8. Rackemann, F. M., and Tobey, H. G.: Studies in Asthma: IV. The Nose and Throat in Asthma, Arch. Otolaryng. **9**:612 (June) 1929.

9. Grant, J. D.: Nasal Disease in Relation to Asthma, Practitioner **90**:914, 1913.

Gottlieb [10] found asthma associated with sinusitis in only 26 per cent of 117 cases. Kern and Schenck [11] found that of 400 cases of asthma there were 70 per cent with clinical evidence and 87.5 per cent with roentgen evidence of disease of the sinuses. Chobot,[12] in studying children up to 15 years of age, found roentgen evidence of sinusitis in 41 per cent of the patients observed in 1930 and in 67 per cent of those observed in 1933.

In a recent study [13] which one of us (R. A. C.) published in 1932 688 cases were studied consecutively, and a complete diagnosis was reached. Nasal examination was made in all, and roentgen examination of the sinuses in 90 per cent, of the cases, and it was found that disease of the sinuses was present in 38 per cent of 257 patients in whom asthma developed between the ages of 10 and 30, in 65 per cent of 171 in whom it appeared between the ages of 30 and 50 and in 83 per cent of 42 in whom it became manifest after they reached 50 years of age. Such figures clearly set forth the importance of disease of the sinuses in asthmatic patients, but when one speaks of asthma of infective origin one does not necessarily imply that the disorder has its origin in disease of the sinuses.

An attack of asthma may be caused by primary acute bronchitis or bronchopneumonia, or it may be secondary to acute—rarely to chronic—tonsillar or pharyngeal lesions with pulmonary and bronchial extension. This is certainly true of infants and young children, whose sinuses are still rudimentary, but the same course of events also occurs in older children and adults. Of the 688 cases which formed the basis of the study referred to, infection was the sole cause of asthma in 34 per cent, and infection combined with sensitization, such as sensitization to pollens, danders or foods, was a cause in an additional 15 per cent; thus a total of 49 per cent of all the cases of asthma were caused by infection.

If one excludes cases of asthma occurring during the first decade of life, since the infections occurring at that age practically always are acute or are secondary to foci in the lymphoid tissue of the pharynx and not in the sinuses, there remain 470 cases; in 248, or 53 per cent, of these infection was a cause, and with the exception of perhaps about

10. Gottlieb, M. J.: Relation of Intranasal Disease in Production of Bronchial Asthma, J. A. M. A. **85**:105 (July 11) 1925.

11. Kern, R. A., and Schenck, H. P.: Chronic Paranasal Sinus Infection: Relation to Diseases of the Lower Respiratory Tract, Arch. Otolaryng. **18**:425 (Oct.) 1933.

12. Chobot, Robert: The Incidence of Sinusitis in Asthmatic Children, Am. J. Dis. Child. **39**:257 (Feb.) 1930; Asthma in Children, ibid. **45**:25 (Jan.) 1933.

13. Cooke, Robert A.: Infective Asthma: Indications of Its Allergic Nature, Am. J. M. Sc. **183**:309, 1932.

8 per cent in which primary pulmonary infection was present, in the rest, or practically 45 per cent (92 per cent of the cases of infective asthma), disease of the sinuses was the important primary focus of the infection causing asthma. The 8 per cent in which disease of the sinuses did not occur included cases of primary acute bronchial and pulmonary infections and of chronic infections with ordinary pathogens as well as with spirochetes and molds.

If one stops to inquire why in certain patients the symptom of asthma is superimposed on nasal and thoracic infections, the only answer that can be made is that these persons have an allergic constitution and become sensitized to bacteria or their products.

The proof of this is found first in the family history. In the study of the 688 cases previously alluded to, a history of allergy in previous generations was found in 45 per cent of 235 cases of purely infective asthma as contrasted with 52 per cent of the 349 cases of asthma due purely to allergy of the "skin-sensitive" type. Further, other allergies existed in 30 per cent of the cases of infective asthma. Again, eosinophilia was present in over 50 per cent of the patients with infective asthma, and eosinophil cells were present in the sputum of practically 100 per cent of the patients whose sputum was examined during an attack. The bronchial mucous membrane is known to be infiltrated with such cells. Eosinophilia was also observed in the discharge from the sinuses and in the hyperplastic sinus membrane of practically all the patients examined.

As a matter of fact, in all the cases of our series in which operation was performed the membrane of the sinuses was of this hyperplastic type. None of the patients with asthma exhibited the true pyogenic membrane associated with suppurative sinusitis, although an acute exacerbation accompanied by discharge of some purulent mucoid exudate was observed from time to time.

Eosinophilia has come to be regarded as a part of the cellular response to the allergic reaction. A more complete survey of this point with the data has been given in the paper [13] on infective asthma.

Another proof of the allergic nature of the infection lies in the capacity of the patients to respond with symptomatic asthma to an injection of vaccine, particularly to injection of an autogenous vaccine.

Of the mechanism of the allergic reactions to bacteria and their products, little is known. Immunologically the manifestation is not at all similar to the reactions to pollen in which an urticarial wheal is formed in the skin immediately as a result of a cutaneous test and an immediate reaction in the membranes results from contact with the pollen such as that which occurs in cases of hay fever and asthma due to an overdose of pollen extract. Also passive transfer of the sensitization is accomplished with the serum of these sensitive patients.

On the contrary, in infective asthma the cutaneous reaction with the bacterial extract or suspension is delayed for from twenty-four to forty-eight hours, if it occurs at all. An overdose of vaccine, if it produces asthma, does so after twelve, twenty-four or even forty-eight hours (symptomatic reaction). There is no passive transfer of the sensitization. What, then, are the facts regarding the cutaneous test with vaccines in cases of asthma? Among 120 patients with infective asthma who have been operated on by one of us (R. C. G.) at the clinic, there were 70 on whom tests with autogenous vaccine were made, and observations were carried out with such care that the results are worth recording. Thirty-eight of these 70 probably had symptomatic asthma due to injection of vaccine, but in 27 an attack of asthma was definitely produced by the injection of vaccine. Nineteen of the 27 gave a delayed positive reaction (from twenty-four to forty-eight hours) to an intradermal test with the vaccine that caused asthma. In none was the immediate reaction positive. Eight of the 27 patients gave negative reactions to the intradermal vaccine which produced asthma.

If one looks at the other side of the picture, there were 32 patients in whom no symptoms of asthma resulted from injections of vaccine, but 25, or 75 per cent, of these gave delayed positive cutaneous reactions to the vaccines. We cannot therefore agree with Thomas and Touart [14] and others who contend that in cases of asthma a diagnostic significance is to be attached to cutaneous reactions to vaccine. It is our opinion that the only reliable test is the reproduction of the asthma and that this symptomatic test presents difficulties and dangers. We believe, therefore, that the cutaneous test is of no value in determining the organism responsible for asthma.

The evidence that disease of the sinuses is the primary focus is to be found in clinical observation on patients with infective asthma and in the results obtained in patients with asthma as a consequence of surgical treatment of the nasal sinuses. In all cases in which it has been possible to observe the development of bacterial asthma in adults, there has been a stage of hyperplastic sinusitis without asthma lasting for from five to ten years or longer. Opportunity to watch this development has been afforded in the large group of patients with hay fever who at first had acute or supposedly acute attacks of sinusitis with the development of hyperplastic changes and often with nasal polypi and who eventually had attacks of bronchitis with each exacerbation of the sinusitis and finally showed signs and symptoms of asthma.

Satisfactory evidence of the primary importance of disease of the sinuses is seen in the effects of surgical treatment of the sinuses on

14. Thomas, W. S., and Touart, M. D.: Late Vaccine Skin Reactions, J. Allergy **4**:242, 1933.

asthma even of many years' duration. The results recorded in the literature at present are not exceeding encouraging. Heatly and Crowe [15] reported improvement in 53 of 62 cases but "only one case was enthusiastic enough to describe himself as 'cured' after three years." However, it is not made clear whether operations on the septum, turbinate bones, tonsils and adenoids were performed alone or in connection with operations on the sinuses.

Rackemann and Tobey [8] reported 91 cases of asthma in which the infection of the sinuses was treated surgically. In 14 per cent cure resulted after a period of more than two years; in 46 per cent improvement occurred; in 31 per cent there was no improvement, and in 9 per cent death occurred. Weille [16] in 1930 stated that of 40 patients treated surgically but 50 per cent have a chance for relatively long continued favorable changes in their asthma. Schenck and Kern,[17] Vaughan [18] and Warner and McGregor [19] reported less favorable results.

But it is difficult from the reports in the literature to evaluate the results of surgical treatment in disease of the sinuses as many cases have not been studied for sensitization, which commonly coexists, and it is not made clear whether the pathologic condition of the sinuses is completely eradicated.

We recently made a study of 120 cases of asthma which included a complete survey of the sensitization and rhinologic conditions. Operations had been performed in all cases, and the postoperative period of observation extended from six months to three and a half years. Patients not reporting within a month have been excluded. Fifty-five cases of infective asthma and 65 of infective asthma associated with allergy of the "skin-sensitive" type constituted the series. These cases have been further divided according to the time since operation into three groups, observed for from six months to one year, from one to two years and from two to three and a half years, respectively. These groups have been further divided into two subgroups: subgroup 1, in which all indicated surgical treatment had been completed, and subgroup 2, in which indicated surgical treatment for one reason or another was still incomplete. The

15. Heatly, C. A., and Crowe, S. J.: Asthma and Infections of the Accessory Nasal Sinuses: A Study Based on Sixty-Two Cases, Bull. Johns Hopkins Hosp. **34**:410, 1923.

16. Weille, F. L.: Studies in Asthma: XVIII. The Surgical Treatment of Chronic Sinusitis in Asthma, J. A. M. A. **100**:241 (Jan. 28) 1933.

17. Schenck, H. P., and Kern, R. A.: An Evaluation of the Therapeutic Effect of the Caldwell-Luc Operation in Bronchial Asthma, J. Allergy **3**:296, 1932.

18. Vaughan, W. T.: Some Rhinologic Aspects of Allergy, J. Allergy **4**:127, 1933.

19. Warner, W. P., and McGregor, G.: Effect of Radical Antrum Surgery on Bronchial Asthma, J. Laryng. & Otol. **48**:595, 1933.

patients with infective asthma only have been treated surgically, and a few have received vaccine therapy in addition. In those with infective asthma associated with allergy as shown by positive cutaneous tests the allergic condition has been taken into account and treated by injection or by elimination.

As shown in table 1, the operations performed were: ethmoidectomy, sphenoidectomy, enlargement of the frontal duct and radical operation on the antrum (Caldwell-Luc type). Rarely was a polypus alone removed, but usually the operation on the sinuses was performed at the same time, because we believe that the source of infection is in the attachment or underlying membrane. Submucous resection and trimming of the inferior turbinates were performed on these patients only in connection with the work on the sinuses or because of marked obstruc-

TABLE 1.—*Pathologic Conditions of the Nasal Passages and Operations on the Sinuses in 120 Cases of Infective Asthma*

Pathologic Conditions	Single	Bilateral	
Chronic sinusitis, ethmoid	21	82	
Chronic sinusitis, maxillary	17	84	
Chronic sinusitis, sphenoid	15	56	
Chronic sinusitis, frontal	30	13	
Chronic sinusitis, with nasal polyps	25	71	
Pansinusitis	..	..	40
Cysts of the antrum	..	..	10
Operations			
Ethmoidectomy	35	58	
Sphenoidectomy	15	28	
Radical operation on the antrum (Caldwell-Luc)	30	27	
Enlargement of frontal duct	6		
Submucous resection	..	..	9
Previous window resection of the antrum	31	17	
Previous operations on the sinuses, ethmoid and sphenoid	..	..	63
Total number of operations on the sinuses	257		

tion, and not as isolated operations for asthma. The greater portion of the middle turbinate was always removed when the ethmoid sinus was exenterated; a smaller portion was removed if the operation was limited to the sphenoid sinus. The usual Caldwell-Luc type of radical operation on the antrum was performed, and we shall not go into any detail about the surgical procedures. The type of operation on the antrum or on the ethmoid or sphenoid sinus is not the important element, but rather the thoroughness with which the procedure is carried out. Nor are we concerned in this paper with the immediate effect of the operation on these asthmatic patients; but we wish to emphasize the fact that even though the operations on the antrum were performed under general anesthesia there was no pulmonary complication in this series, and, with the exception of one case, there was no operative shock. Too many general practitioners, as well as some rhinologists, are appalled by the word "radical" attached to this opera-

tion and therefore will not recommend its performance. However, this need not be, and we suggest that the procedure be called simply the "complete" operation on the antrum.

There were no cases in which there was sufficient pathologic evidence to justify an external operation on the frontal sinus, although in several cases enlargement of the intranasal frontal duct was performed with good results. The intranasal operation, ethmoidectomy or sphenoidectomy, if needed, was first performed with the patient under local anesthesia, and on the following day, or as soon as the general condition of the patient permitted, the complete Caldwell-Luc operation on the antrum was performed. Our results show that when the intranasal operation and the operation on the antrum are both needed one procedure alone seldom suffices, and we believe that operations on the antrum, for example, frequently produce unsatisfactory results because a diseased ethmoid or sphenoid sinus is not treated properly at the same time.

The intranasal operation can often be performed bilaterally at one sitting. Also both antrums may be radically operated on in a single procedure.

Infection of the ethmoid sinuses was associated with infection of the sphenoid sinus in 65 cases and with infection of the antrum in 95 cases. The sphenoid sinus was seldom involved without coexistent involvement of the ethmoid sinuses or of the antrum. The frontal sinus was least frequently involved. One antrum alone was involved in 17 cases; the involvement was bilateral in 84 cases. In 80 per cent of our 120 cases nasal polypi were present. The high percentage may have been due to the fact that a large majority of the patients had undergone nasal operations previously and that patients with polypi come to operation more frequently than others.

The ethmoid and sphenoid sinuses were operated on jointly in 38 cases, 28 of the operations being bilateral. Thirty patients had a single Caldwell-Luc operation, and 27, a bilateral operation; 21 had unilateral operations on the ethmoid sinus and antrum, and 20 bilateral operations on these cavities. Operation on the ethmosphenomaxillary group was performed unilaterally in 10 cases and bilaterally in 12.

The interesting points brought out in this follow-up study of the postoperative course of our patients (table 2) are as follows:

1. Eighty-four, or 70 per cent, of the entire series showed definite improvement.

2. Of those who had received complete surgical treatment (subgroup 1), 86 per cent showed improvement, as contrasted with 39 per cent, the figure for those on whom the surgical treatment was incomplete (subgroup 2).

3. Considering only the groups who received complete surgical treatment, cure or nearly complete cure (table 2) occurred in 29 per cent of the patients in the group from six months to one year, in 36 per cent of those followed for from one to two years (group 2) and in 51 per cent of those followed for from two to three and a half years (group 3).

TABLE 2.—*Analysis and Results in 120 Cases of Infective Asthma with Disease of the Sinuses Surgically Treated* *

Postoperative Follow-up Period	Results +	Results ++	Results +++
Asthma (120 cases)			
Infective asthma (55 cases)			
Complete surgical treatment (34 cases): 6 months to 1 year	2	4	2
Complete surgical treatment (34 cases): 1 to 2 years	3	6	3
Complete surgical treatment (34 cases): 2 to 3½ years	1	3	10
Incomplete surgical treatment (21 cases): 6 months to 1 year	3	1	0
Incomplete surgical treatment (21 cases): 1 to 2 years	3	1	0
Incomplete surgical treatment (21 cases): 2 to 3½ years	7	4	2
Asthma combined with allergy (65 cases)			
Complete surgical treatment (45 cases): 6 months to 1 year	2	4	3
Complete surgical treatment (45 cases): 1 to 2 years	1	6	6
Complete surgical treatment (45 cases): 2 to 3½ years	2	12	9
Incomplete surgical treatment (20 cases): 6 months to 1 year	5	0	0
Incomplete surgical treatment (20 cases): 1 to 2 years	1	0	1
Incomplete surgical treatment (20 cases): 2 to 3½ years	6	5	2
	36	46	38

	Complete Operation +	Complete Operation ++ and +++	Incomplete Operation +	Incomplete Operation ++ and +++
Infective asthma (total number of cases)	6	28	13	8
Asthma combined with allergy (total number of cases)	5	40	12	8
Results (total number of cases)	11	68	25	16
		or 86% improvement		or 39% improvement
Improvement in total number of cases (120)			36	84
				or 70%

Duration	Number of Cases	Results, ++ and +++	Percentage
½ to 1 year	26	14	53
1 to 2 years	31	23	74
2 to 3½ years	63	47	75

* The symbol + indicates slight or no improvement in asthma; ++, definite improvement; +++, no asthma or a rare attack.

On the other hand, results designated as slight improvement and definite improvement (table 2), which really represent the total improvement, occurred in 77 per cent, 85 per cent and 91 per cent, respectively, in the three groups. The fact that the percentages increased with the passage of time from operation is perhaps the most hopeful point to be gleaned from these studies. We do not anticipate any striking results in the first six months, and we have not even considered such

results in our study. The frequent lack of immediate improvement and the gradual improvement with the passage of time indicate to us the deep-seated nature of the infection with which allergy exists, the seat of that infection probably being located in the bronchial glands and the mucosa. After removal of the primary focus these secondary foci heal slowly. The patients who do well from the beginning and remain well for three and a half years may never have had such bronchial involvement. In those who never do well after complete surgical treatment the capacity of the secondarily involved glands to heal appears to be lacking. It ought to be possible to determine whether or not such assumptions are correct, and some of our present studies are being directed to that end.

The fact that in 12 cases in which window resection of the antrum had been performed the complete operation on the antrum later became necessary because of continued asthma and that in 9 of these definite improvement then occurred is a strong point in favor of the complete operation when indicated. Also we noticed that after window resection the passages became blocked frequently by the continued growth of polypi in the antrum and that infections of the upper portion of the respiratory tract necessitating treatment of the sinuses were more frequent before than after the complete operation. Furthermore, when the indicated surgical treatment had been completed, the patients who later had an acute infection of the upper portion of the respiratory tract frequently did not have a recurrence of attacks of asthma. We[1] have previously presented evidence that the infection is in the deeper layers of the membrane of the sinuses and that to eliminate this an operation more extensive than simple window resection is needed. The improvement in general health, that is, in weight, appetite, strength, morale and such associated conditions as arthritis, was quite striking in at least 50 cases. The condition of the sinuses, which is important to the patient regardless of asthma, was entirely satisfactory in 100 cases at the last examination, while in 20 cases there was a recurrence of polypi. In 14 of the latter cases surgical treatment had been incomplete.

In evaluating the effect of surgical treatment of the sinuses on asthma it is essential to analyze the case thoroughly not only for the completeness of the elimination of nasal infection by operation but also as to the extent of the treatment of any associated allergy of the "skin-sensitive" type and any continuing extranasal infection. Infection with molds (fungi) and spirochetes, and tuberculosis and infections of the teeth and tonsils are important complicating factors in cases of infective asthma. This is well illustrated by the fact that 6 of our patients who showed no improvement had a complicating bronchial moniliasis that did not respond to any treatment.

Two of our patients also seemed to do well after ovarian and uterine operations, although we were unable to evaluate the result properly because of the previous operations on the sinuses. Certainly we have found that in some cases, as far as prolonged freedom from asthma is concerned, dust and other allergens may be important factors and cannot be neglected simply because the patient has had some pathologic condition of the sinuses and has been operated on.

SUMMARY

In asthma, disease of the sinuses is an important primary focus of infection. Of 248 cases of infective asthma beginning after the patient was 10 years of age, sinusitis was an etiologic factor in 92 per cent.

We believe that infective asthma is the result of an allergic reaction to bacteria or their products. This is evidenced by the frequency of allergy in the preceding generations, by the associated allergies, by the eosinophilic response of the membranes of the sinuses, by the condition of the exudate, sputum and blood and, lastly, by the reproduction of symptomatic asthma through injections of vaccine.

Cutaneous reactions to vaccine cannot be relied on to determine the organism causing asthma.

One hundred and twenty patients with asthma associated with disease of the sinuses which was treated surgically were observed postoperatively for from six months to three and a half years. In 70 per cent of the patients improvement occurred. We believe that results should be evaluated according to the completeness or incompleteness of the surgical procedure since 86 per cent of the patients who received complete surgical treatment (subgroup 1) showed improvement as contrasted with 39 per cent, the figure for those on whom surgical treatment was incomplete (subgroup 2). Striking results should not be expected too soon after operation. Increasing percentages of improvement were noted in our series with the passage of time, probably owing to the gradual elimination of infection in the deep-seated bronchial glands or mucosa.

In analyzing the effect of surgical treatment of the sinuses in asthma, extranasal infections, such as those due to molds (fungi) or spirochetes, as well as any associated allergy of the "skin-sensitive" type, must be considered.

PYOTHORAX DUE TO FUSOSPIROCHETAL INFECTION

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Fusiform bacilli and Vincent's spirilla are frequently credited with causing severe infections in the mouth and pharynx. During the last few years a number of cases have been reported in which fusospirochetal infection was considered responsible for severe pulmonary infection.

Since the first descriptions of the fusospirochetal organisms by Plaut [1] in 1894 and Vincent [2] in 1899, the organisms have been known to exist in the upper respiratory tract in the absence of any evidence of acute infection. Controversy still exists as regards the pathogenicity of these organisms. Smith [3] has experimented at length and has reported that so-called fusospirochetal pulmonary infections are probably due to a symbiosis of a spirochete, a fusiform bacillus, a vibrio and a coccus. Lichtenberg, Werner and Leuck,[4] who recently reviewed the literature in regard to authentic proof of the pathogenicity of these organisms and reported experimental data of their own, concluded that the pathogenicity of the fusospirochetal organisms is still open to question. Nevertheless cases are numerous in which clinical signs follow fairly characteristic patterns and in which bacteriologic examinations demonstrate that the fusospirochetal organisms are greatly in preponderance. With full realization that fusospirochetal infection may or may not be a true bacteriologic entity, I wish to report three cases in which pyothorax accompanied severe pulmonary infection and in which fusospirochetal organisms appeared to constitute the important etiologic factor.

The clinical course in the cases reported indicates that pyothorax associated with large numbers of fusospirochetal organisms causes certain clinical signs not encountered in the more common types of

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From the Department of Medicine, the Arnett-Crockett Clinic.

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2. Vincent, M. H.: Recherches bactériologiques sur l'angine à bacillus fusiformis, Ann. Inst. Pasteur **13**: 609, 1899.

3. Smith, D. T.: Fusospirochetal Disease of the Lungs Produced with Cultures from Vincent's Angina, J. Infect. Dis. **46**: 303 (April) 1930; Relation of Vincent's Angina to Fusospirochetal Disease of the Lungs, J. A. M. A. **94**:23 (Jan. 4) 1930.

4. Lichtenberg, H. H., Werner, M., and Leuck, E. V.: The Pathogenicity of the Fusiform Bacillus and Spirillum of Plaut-Vincent, J. A. M. A. **100**:707 (March 11) 1933.

pyothorax. It is felt that diagnosis of this type of pyothorax should receive particular attention, as the treatment should be directed along lines different from the medical and surgical treatment of the more common types of pyothorax. The establishment of a diagnosis of pyothorax resulting from fusospirochetal infection may precede the proper identification of the underlying infection involving the parenchyma of the lungs and may be of great value in the true estimation of the prognosis of the case.

REPORT OF CASES

CASE 1.—Miss M. B., aged 29, was admitted to the hospital on Oct. 13, 1933. Her chief complaint was frequent cough with expectoration of moderate amounts of purulent sputum for three weeks. She had continued with her regular work as technician in a laboratory until one week before admssion to the hospital, when she went to bed because of general malaise and slight fever. Twelve hours before admission she had a moderate chill, after which her temperature rose to 102 F. She had had frequent bronchial colds and a chronic cough since early childhood. She had pneumonia on three occasions between the ages of 3 and 18 years. Tonsillectomy was performed at the age of 24, at which time the patient was first treated for chronic maxillary sinusitis. Since the age of 15, she had occasionally coughed up small amounts of blood-tinged sputum, the hemorrhages occurring more frequently and increasing in volume during the previous five years. Repeated examination failed to reveal any evidence of tuberculous infection. At the age of 25 iodized poppy-seed oil 40 per cent was first used in examination of the bronchial tract, and rather extensive bilateral bronchiectasis was demonstrated. During the three years previous to the present illness the patient had expectorated from 3 to 4 ounces (88.5 to 118 cc.) of purulent sputum during the latter part of each forenoon and again during the latter part of each afternoon.

On admission to the hospital the temperature was 102 F., the pulse rate 96 and the respiratory rate 20. Examination gave essentially negative results except in the chest, in which harshness of breath sounds was noted and a few coarse, moist râles were heard over the lower half of each lung posteriorly. The leukocyte count was 21,800. The temperature remained constant at 102 F., and on the third day in the hospital a small area of dulness and pneumonic breathing was noted at the base of the right lung. The patient had a frequent harsh bronchial cough and raised small amounts of purulent sputum. Examination of the sputum revealed many pneumococci and streptococci. The temperature dropped to normal on the fifth day in the hospital, and the patient felt much better generally, the respiratory rate remaining the same. After remaining normal for two days, the temperature again became elevated, varying intermittently between 100 and 102 F. On the ninth day in the hospital the patient first complained of pain in the lower part of the chest on the right side on inspiration.

A roentgenogram of the chest showed some increased density at the base of each lung, with evidence of lobular pneumonia at the base of the right lung. The leukocyte count was 16,900. The patient continued to have moderately severe pain in the lower part of the chest on the right side on inspiration which was relieved by doses of ½ or 1 grain (0.032 or 0.065 Gm.) of codeine. On the morning of the fourteenth day in the hospital the patient had a rather sudden onset of excruciating pain in the lower part of the chest on the right side, and general physical signs of severe shock developed rapidly. The temperature rose to 104.4 F.,

and the pulse rate was accelerated to 130, with very poor pulse volume and marked cyanosis. The respiratory rate increased to 40, with very shallow, gasping respirations. Strapping of the right side of the chest with adhesive tape eased the pain slightly. The patient was placed in an oxygen tent, whereupon the cyanosis disappeared and the temperature and pulse rate showed a decline. Frequent doses of morphine gave partial relief from the pain. The patient remained in the oxygen tent, and the immediate prognosis was considered grave because of her general weakened physical condition. There was a frequent cough, which greatly aggravated the pain in the chest.

On the twentieth day physical examination revealed some effusion in the right pleural cavity. This did not increase in amount until the twenty-fourth day, when there was evidence of a rapid increase in amount, with marked difficulty in breathing when the patient lay on the opposite side. The leukocyte count was 28,800. A roentgenogram of the chest showed complete obscuration of the right pulmonary field, with moderate displacement of the heart and mediastinum to the left. Thoracentesis was performed, and 630 cc. of thin greenish-yellow pus was aspirated from the right pleural cavity. The pus was characterized by an extremely foul odor, and on bacteriologic examination it was found to contain many pneumococci and streptococci and large numbers of fusiform bacilli and Vincent's spirilla.

Thoracotomy was considered inadvisable because of the general weakened condition of the patient and because of the very thin consistency of the empyema fluid. On the twenty-ninth day in the hospital 540 cc. of fluid was aspirated from the right pleural cavity, all the fluid being removed that could be aspirated through an 18 gage needle. On the following day a small trocar was inserted between the ribs and into the right pleural cavity, and through the trocar was inserted a small rubber catheter to which a flap valve was attached. Several ounces of pus drained from this tube, but within an hour the respirations became very shallow, the heart tones became progressively weaker, and the patient died.

Autopsy revealed evidence of pneumonia in the left lung involving the lower lobe and the apex and a moderate degree of bronchiectasis. The right lung was in complete collapse and showed marked bronchial and broncheolar dilatation throughout the lower lobe. The lower lobe contained many small bronchiectatic abscesses. These abscesses contained light green pus similar in bacteriologic characteristics to the pus aspirated from the right pleural cavity prior to death.

Case 2.—Mr. F. M., aged 34, a sergeant in the United States Army, was admitted to the hospital on Feb. 6, 1934. He had had general malaise and pains in the lower part of the chest on the left side on inspiration five days before admission to the hospital and had been in bed for three days with moderate fever. The pains in the chest had become progressively more severe, and it was for the relief of this symptom that hospitalization was advised. The patient had had frequent "colds" for several years and since May 1930 had been treated for chronic maxillary sinusitis on numerous occasions.

On his admission to the hospital the temperature was 101 F., the pulse rate 120 and the respiratory rate 34. Examination of the nose and throat revealed moderate pharyngeal redness and a small amount of mucopurulent postnasal dripping. Expansion of the chest was diminished on the left side, and percussion revealed flatness over the left lung below the level of the sixth dorsal vertebra. Breath sounds and fremitus were absent over the area of impaired resonance. The right lung revealed no abnormalities other than some displacement of the right cardiac border to the right. Examination of the urine revealed a trace of albumin and a few pus cells. The leukocyte count was 22,200, with 80 per cent polymorphonu-

clears and 20 per cent lymphocytes. The Schilling index was 10.4. A roentgenogram of the chest showed the entire left side to be full of fluid, with considerable displacement of the heart and mediastinum to the right. No lung structure could be seen on the left side. The right lung was compressed but was normal otherwise. On the second day in the hospital thoracentesis was performed, and 900 cc. of straw-colored fluid was removed from the left pleural cavity. Examination of this fluid failed to reveal organisms, and no growth was obtained on culture. The patient had a moderately severe bronchial cough and produced small amounts of mucopurulent sputum. He complained of severe pain in the left side of the chest on inspiration and on coughing, the pain not being relieved by 1 grain doses of codeine administered hypodermically. The fever ran an intermittent course, the temperature varying from 101 to 103 F. The patient showed no respiratory embarrassment, and after the first thoracentesis physical examination failed to reveal evidence of displacement of the mediastinum. On the eighth day in the hospital the leukocyte count was 20,800. On the eleventh day a second roentgenogram of the chest showed the left side of the chest still filled completely with effusion but no displacement of the heart and mediastinum. The right lung showed no pathologic change. The leukocyte count at this time was 32,300. As the temperature was still varying between 101 and 103 F., and leukocytosis was more marked and the patient's general condition was not improving, thoracentesis was repeated on the twelfth day. The fluid, which was obtained from the left pleural cavity, was greenish-yellow pus of moderately thin consistency and with an extremely foul odor. Only a small amount of this pus was aspirated and on the fourteenth day in the hospital a thoracotomy was performed, after which large amounts of the pus drained from the cavity. Examination of this pus revealed large numbers of small bacilli morphologically similar to Bacillus influenzae, fusiform bacilli and Vincent's spirilla. Following the thoracotomy the fever showed a rather rapid decline, the temperature being within 1 degree of normal after the seventeenth day. However, at noon on the twenty-second day in the hospital, on getting out of bed the patient suddenly became very weak and pale. He perspired profusely and was markedly dyspneic. The pulse volume was very poor, and cyanosis developed within a few minutes. With oxygen therapy the cyanosis cleared up and the respirations became less labored. Physical examination revealed no evidence of collapse of the lung. The heart tones became progressively weaker, and the patient died one and one-half hours later.

Case 3.—Mr. G. I., a railway official aged 52, was admitted to the hospital on March 14, 1934. His complaint was excruciating pain in the left side of the chest which was worse on inspiration. He had had a moderate "cold" with a slight cough for a week and had experienced some slight to moderately severe pain in the left side of the chest, which was worse on inspiration, during the preceding three days. He had not noted any fever and had attended to the work in his office up to the day of admission to the hospital. On that day he had awakened at 3:00 a. m. with moderately severe pain in the left side of the chest. After two hours the pain became more severe, and at 8:00 a. m. he called a physician. The physician found the patient pale, perspiring and walking the floor, being unable to stay quiet in bed because of the severe pain. The temperature was subnormal, and the pulse rate was 90. During the next two and a half hours 1 grain of morphine was given hypodermically in three doses but gave only partial relief from the pain. The patient was then taken to the hospital in an ambulance. On his admission to the hospital the temperature was 98 F., the pulse rate 110 and the respiratory rate 20. Urinalysis revealed no abnormalities. The leukocyte count was 22,700, with 94 per cent polymorphonuclears. The Schilling index was

5.7. The temperature rose to 99.6 F. during the afternoon, and the patient continued to have some pain in the left side of the chest on inspiration, requiring morphine twice during the first twenty-four hours. In the afternoon of the second day in the hospital the temperature increased to 101.8 F., with the pulse rate 110 and the respiratory rate 28. At this time pneumonic breathing was heard over the lower part of the chest on the left side in the posterior axillary line. A roentgenogram of the chest showed evidence of pleural effusion on the left side but no evidence of parenchymal abnormalities. The temperature varied from 100 to 102 F., and morphine was needed every six to twelve hours to ease the pain in the chest. A moderately frequent cough was present, but no sputum was raised. On the fourth day the leukocyte count had increased to 34,000, with 93 per cent polymorphonuclears; the Schilling index was 2.4. Physical examination revealed an effusion of the left pleural cavity filling the lower half of the chest on the left side. On the eighth day in the hospital thoracentesis was performed, and 700 cc. of moderately thin pus was removed from the left pleural cavity. The pus was light green and had a very foul odor. Bacteriologic examination of the pus revealed large numbers of fusiform bacilli and Vincent's spirilla, no other organisms being found. The patient's general condition was so poor that thoracotomy was considered inadvisable. Therefore a small rubber catheter was introduced through a trocar into the left pleural cavity through the eighth intercostal space in the posterior axillary line, and constant drainage of the empyema was established. The fluid drained freely, but the patient continued to require morphine frequently for pain in the left side of the chest. The leukocyte count on the eleventh day in the hospital was 19,800, with 81 per cent polymorphonuclears, but the temperature was higher, varying intermittently from 99 to 103 F. On the fourteenth day there was a sudden onset of severe, sharp pain in the left side of the chest, with profuse perspiration, slight cyanosis, rapid shallow breathing and a marked increase in the rate and decrease in the volume of the pulse. Physical signs indicative of pneumothorax were present over the lower portion of the left side of the chest. During the following week the patient was very weak, but the temperature was lower, the maximum never exceeding 101 F. The left pleural cavity was irrigated daily with saline solutions, and moderate quantities of thick pus drained through the catheter. The leukocyte count on the eighteenth day in the hospital was 20,600, with 69 per cent polymorphonuclears; the Schilling index was 5.3. On the twenty-second day the temperature was higher, varying from 99 to 102 F., and the leukocyte count was 23,500, with 79 per cent polymorphonuclears. On the twenty-fourth day in the hospital a roentgenogram of the chest showed a small amount of fluid in the left pleural cavity. There were marked pleural thickening on the left side and complete collapse of the left lung. No pathologic change was noted on the right side. It was thought that drainage of the left pleural cavity was unsatisfactory owing to the thick consistency of some of the purulent exudate and the small caliber of the intercostal drain. The patient had shown a slow increase in strength following the development of the pneumothorax, and on the twenty-seventh day thoracotomy was performed with no untoward reaction. Satisfactory drainage was established, and the temperature showed a slow decline until it reached normal on the fifty-second day. The leukocyte count was 22,750 on the forty-third day and had decreased to 12,250 on the fifty-eighth day. The amount of drainage of empyema fluid gradually decreased and was very slight at the time the patient was discharged on the sixty-eighth day after he was admitted to the hospital.

The administration of neoarsphenamine intravenously was started the day after the thoracentesis was performed which established the diagnosis of empyema caused

by fusospirochetal infection. Five doses of 0.3 Gm. each were given at intervals of from seven to ten days during the remainder of the patient's stay in the hospital. One dose was given two weeks after he was discharged.

Eight days after the patient was discharged from the hospital a roentgenogram of the chest showed a rather large pneumothorax on the left side with a small amount of effusion at the base of the lung. The right lung appeared normal. At this time the leukocyte count was 13,600, with 70 per cent polymorphonuclears; the Schilling index was 10.7.

The patient was last seen eight weeks after discharge from the hospital, at which time a very small amount of pus was draining from the thoracotomy opening. The leukocyte count was 11,000. The patient was taking a moderate amount of physical exercise and was feeling well.

COMMENT

In two of this series of three cases definite evidence of infection involving the parenchyma of the lungs was present prior to the development of pyothorax. It is believed that the fusospirochetal infection was secondary, first in the parenchyma of the lung and later in the pleura.

I have not observed inspiratory thoracic pain of such severity in other types of pulmonary infection, and in no other cases have I observed the persistence of the pain long after the development of pleural effusion. The persistence of severe pleural pain after the development of effusion should make one suspect the presence of fusospirochetal infection.

In all the cases of this series the pus drained from the pyothorax possessed a very foul, fetid odor. In none of the cases did the sputum possess this odor, nor was the breath fetid. It is believed that a localized area of pulmonary gangrene developed prior to the development of the pyothorax. In cases 1 and 3 it is believed that the occurrence of spontaneous pneumothorax aided materially in the control of the acute infection involving the parenchyma of the lung.

Marked leukocytosis was observed in all the cases, the maximum count varying from 28,800 to 34,000.

In all the cases reported oral hygiene had been good. In case 1 there was a chronic bronchiectatic condition, and in case 2 chronic maxillary sinusitis was present, and it is presumed that in both cases fusospirochetal organisms were present in the respiratory tract. In case 3 there were no history and no physical evidence of oral infection or infection of the upper respiratory tract prior to the onset of the illness reported.

In two of the cases the general condition of the patient was so grave that following the establishment of the diagnosis of pyothorax thoracotomy was considered inadvisable. In these cases an intercostal drain was installed, and thoracotomy was performed later, at a time when the patient's condition had improved. It is believed that such conservative treatment is justified.

In only one case was arsenic therapy used. In case 3 neoarsphenamine was administered intravenously at regular intervals from the time of the diagnosis of fusospirochetal infection throughout the acute stage of the infection. It is believed that neoarsphenamine should be administered intravenously at regular intervals in every case of acute fusospirochetal infection.

SUMMARY

Three cases of acute pulmonary disease with pyothorax due to fusospirochetal infection are reported.

The diagnosis was established only after the presence of fusospirochetal organisms in the empyema fluid was observed.

Attention is called to the severity of the pleural pain and to the fact that the pain persists after the development of pleural effusion.

The fetid odor of the pus obtained from the pyothorax in this type of infection is considered of diagnostic importance.

It is believed that this type of acute pulmonary infection is much more common than a survey of the medical literature would indicate, and a plea is made for more consideration of this type of infection in the differential diagnosis of cases of acute pulmonary disease.

Progress in Internal Medicine

GASTRO-ENTEROLOGY IN 1934

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In surveying the literature on gastro-enterology for 1934 it has been my aim to present abstracts of only those articles which might be of interest and of practical value to the general practitioners of medicine who are familiar with the wide variety of gastro-intestinal disorders. In following such a plan, certain textbook subjects, such as cancer of the stomach and appendicitis, concerning which the usual large number of articles have appeared, have been discussed but briefly, because practically nothing new has been written about them. As some diseases have been given considerable attention and others none, the consequence is an unbalanced review of the very extensive field of gastro-enterology. But it is hoped that the elimination of reports on subjects which contribute little or nothing to the advancement of the knowledge but are often included for the sake of completeness will give the reader a clearer and more concise insight into the progress made in this field during the past year.

ESOPHAGUS

Under the heading "Some Disorders of the Esophagus," Hurst [1] describes four syndromes which he considers relatively new and not uncommon. He believes that every physician has encountered them and will be better able to recognize them in the future. The first of these he terms dysphagia of anemic women. There is anemia of the hypochromic type, often associated with deficient gastric acidity and occasionally with splenomegaly. Atrophic glossitis is constantly present, which is identical in every respect with the glossitis of pernicious anemia described by Hunter. Hurst believes that the dysphagia is a result of a disturbance in the neuromuscular mechanism, causing relaxation of the normally closed pharyngo-esophageal sphincter. He designates this achalasia and says that it is caused by a spread of the atrophic inflammation of the mucous membranes in the neighborhood to involve either the nerve endings or the ganglion cells of Auerbach's plexus, which control the sphincter. There is no pathologic proof of such an etiology.

1. Hurst, A. F.: Some Disorders of the Esophagus, J. A. M. A. **102**:582 (Feb. 24) 1934.

The anemia responds rapidly to the administration of iron, and the dysphagia can be cured by the passage of bougies weighted with mercury.

The syndrome actually differs from simple achlorhydric anemia only by the presence of the complicating dysphagia. Hurst points out that the name Plummer-Vinson's syndrome, which he gave it in 1926, is not justifiable, as it was first described by Kelly and by Paterson in 1919.

The second syndrome described is not new, but Hurst's interpretation of the underlying cause gives a new conception of a well recognized condition. He describes so-called cardiospasm as achalasia of the cardiac sphincter. The enormous dilatation and hypretrophy of the esophagus, thought to be due to spasm of the cardiac sphincter, are in reality due to a loss of proper relaxation of the sphincter, or achalasia. Convincing evidence is presented that this assumption is correct and that the etiology is chronic inflammation of Auerbach's plexus in this region, which causes a lack of the normal relaxation response of the sphincter. Dilatation by the mercury tube effects a cure in the large majority of cases. If operation is necessary, the procedure of choice is stretching the sphincter from below by introducing the fingers through the stomach. An interesting and historic report of a case by Thomas Willis, published in 1672, is included, which presents the theory of achalasia as opposed to that of cardiospasm.

The third syndrome is that of chronic peptic ulcer of the esophagus. As this has been more adequately described in a separate article, it will be reviewed subsequently. The fourth syndrome has been designated the recurrent hiatus syndrome of von Bergmann. The tissues around the hiatus oesophageus must be abnormally lax so as to permit the formation of a diaphragmatic hernia. This may be congenital, but the preponderance of its occurrence in elderly persons suggests that it is not. It is to be clearly differentiated from the familiar type of nontraumatic diaphragmatic hernia which results from congenital shortness of the esophagus. The hernia is generally intermittent, being produced by increased intra-abdominal pressure. Characteristically the hernia occurs when the patient bends over or lies prone. It may produce a variety of symptoms, the chief of which seems to be intermittent pain or pressure under the xiphisternum, usually nocturnal at the onset. Vomiting is sometimes the only symptom. An attack is relieved when the patient sits up or stands or when the stomach is distended with an aerated drink. The technic of the roentgen examination is of the utmost importance. The hernia ordinarily can be demonstrated only while the patient is lying down, and the barium sulphate meal should be administered with the patient on his back. When the patient stands up, the hernia disappears. Only a clinical knowledge of the manifestations of

recurrent hernia of the hiatus will lead to the special type of roentgen examination necessary to disclose this rare form of herniation. Treatment must be directed to the avoidance of anything that is likely to increase intra-abdominal pressure.

Cunha [2] reports 2 cases of the recurrent "hiatus hernia" syndrome of von Bergmann and stresses the symptomatology and the treatment. Reproductions of the roentgenograms showing the hernias are included, with the notation that they were taken with the patient in the recumbent position and that the hernia of the hiatus could not be visualized with the patient in the upright position. The symptoms may resemble those of ulcer or disease of the gallbladder. The most prominent symptom is substernal distress or pressure, and dysphagia may be experienced. In Cunha's cases the complaint was of food passing up and down the esophagus and seemingly not entering the stomach. Pain is often substernal or sharply localized in the midportion of the epigastrium and may be referred through to the back. Nocturnal distress while the patient is lying in bed with relief when the patient sits erect is frequent. Inflammation of the involved area and ulceration of the lower end of the esophagus may occur. On roentgen examination, repeated observations may be required to demonstrate the lesion; having the patient carry on forced deep inspiration may be of distinct aid in visualization of the hernia. The treatment outlined is largely symptomatic. The avoidance of both external and internal factors which may lead to an increase of intra-abdominal pressure is emphasized.

Under the heading "Thoracic Stomach," Goodall and Hoyt [3] report 5 cases of congenitally short esophagus, with a part or all of the stomach above the diaphragm. The condition in these cases is to be carefully distinguished from true hernia of the diaphragm and from the protrusion of small portions of the stomach through the esophageal opening of the diaphragm when the esophagus is of normal length. The authors could find reports of only 7 similar cases in the literature, although they believe that a good many cases reported as instances of hernia of the diaphragm were probably cases of congenitally short esophagus with thoracic stomach. An exact diagnosis must depend on detailed roentgen studies.

The symptoms of thoracic stomach are due to: (1) interference with normal peristalsis of the gastro-intestinal tract and (2) embarrassment of the thoracic organs. The symptoms may arise in early life and persist until death. Cardiorespiratory symptoms predominate when the greater part of the stomach is above the diaphragm, and they have a

2. Cunha, F.: Recurrent "Hiatus Hernia" Syndrome of von Bergmann, Am. J. Digest. Dis. & Nutrition **1**:170, 1934.

3. Goodall, H. W., and Hoyt, L. H.: Thoracic Stomach: Report of Five Cases, Arch. Int. Med. **53**:594 (April) 1934.

tendency to appear late in life. Dyspnea on ordinary activity is a characteristic finding. It rapidly disappears when the patient is at rest. A sense of substernal fulness is common if the patient overeats and is immediately relieved by vomiting. The real digestive symptoms are those of persistent hyperacidity, and they may be complicated by the presence of an ulcer. Attacks of abdominal pain, nausea and vomiting may occur. Anemia occurred in 1 case, but a duodenal ulcer was found on postmortem examination.

The problem of treatment belongs to the field of the internist and not to that of the surgeon, for the short esophagus cannot be corrected. Therapy is, for the most part, dietary, and a complete regimen similar to that instituted in cases of peptic ulcer may be necessary.

Chronic peptic ulcer of the esophagus is rare. Hurst [4] reports 3 more cases to be added to the literature, in 2 of which the ulcer was demonstrated by roentgen examination. Usually this lesion can be diagnosed only by esophagoscopic examination. Discomfort or pain occurs under the lower end of the sternum while solid food is being eaten or, less frequently, half an hour or more after meals. It often radiates to the back. At first, pain is not caused by the ingestion of soft foods and liquids, lasts only a few minutes and is relieved by alkalis. Later, the pain is prolonged and is followed by regurgitation. The patient is afraid to eat. Severe hematemesis, perforation or obstruction may occur. An esophageal ulcer has all the anatomic characteristics of a chronic ulcer of the stomach or duodenum. It always occurs just above the cardiac sphincter, apparently in an area of heterotopic gastric mucous membrane. The treatment is similar to that given in cases of peptic ulcers which occur elsewhere. Obstruction may require gastrostomy.

STOMACH

Gastric Physiology.—The study of gastric physiology seems to attract the attention of an ever increasing number of investigators. Most of the knowledge of the functions of the stomach can be traced to laboratory experimentation on animals and on man, and much that is of interest and of promise in the field of gastro-enterostomy has been published by research workers. It behooves the internist to try to keep pace with the physiologist and apply the latter's knowledge to the practice of medicine. With this in mind, a few papers dealing with a number of different problems in gastric physiology have been included in this review.

Experimental data concerning the influence of the sympathetic nervous system on the secretory activity of the stomach are scarce and

4. Hurst, A. F.: Chronic Peptic Ulcer of Esophagus, Guy's Hosp. Rep. **84**: 104, 1934.

controversial. Although the results of Baxter's investigations [5] in this field on dogs and cats cannot necessarily be applied in their entirety to man they are of particular interest because of their bearing on the rationale of mucin therapy of peptic ulcers and because of the possible effects on gastric secretion of splanchnectomy for high blood pressure. It has been stated that sympathetic fibers may both excite and inhibit gastric secretion and that their effect on the fundus of the stomach may differ from that on the pylorus, particularly as regards the secretion of mucus. There are also differences of opinion as to the influence of epinephrine on secretion. Baxter has devised a number of complicated operations on animals in an effort to solve these problems. He concludes from his experiments that long continued rhythmic stimulation of the splanchnic nerves produces a steady secretion of alkaline mucus possessing a low digestive power. Repeated injections of epinephrine had a similar effect. The "paralytic secretion" of alkaline mucus which follows the section of the splanchnic nerves probably depends on an altered vascularization of the stomach. All parts of the stomach secrete mucus, the pylorus being the chief source of secretion, the body of the stomach serving as a less prolific source and the fundus contributing very little. A weak stimulation of the vagus nerve also produces a secretion of mucus from the stomach of the dog and of the cat. Further experiments have established the fact that the sympathetic nervous system does not play an essential part in the first, or nervous, phase of gastric secretion. It has long been known that this phase is mediated chiefly by the parasympathetic nervous system.

For a number of years Hollander [6] has been studying the physiology of gastric secretion. In a recent article, "The Composition of Pure Gastric Juice," he reviews the results of much previous experimental work in this field and endeavors to correlate them with more recent observations. Of particular interest is the precise quantitative evidence he offers of the constant acidity of gastric juice as it flows from the glands. This is in accord with Pavlov's theory and contrary to the Rosemann theory of variable acidity of the parietal secretion, in which the acidity is integrally related to the rate of its formation. It seems probable that Hollander's studies have settled this controversial problem, although in the absence of reliable information concerning the composition of the alkaline component of gastric secretion the final word on constant acidity may not yet have been said.

5. Baxter, S. G.: Sympathetic Secretory Innervation of the Gastric Mucosa, Am. J. Digest. Dis. & Nutrition **1**:36, 1934; Role of the Sympathetic Nervous System in Gastric Secretion, ibid. **1**:40, 1934.

6. Hollander, F.: The Composition of Pure Gastric Juice, Am. J. Digest. Dis. & Nutrition **1**:319, 1934.

Gianturco,[7] working at the Mayo Foundation, has carried out a new type of experimental study on the mechanics of gastric activity. He used trained cats as experimental animals, as their stomachs are strikingly similar to the stomach of man. Most of the experiments were carried out by means of roentgen rays, the usual form of contrast mediums being utilized. In order to observe the movements of the visceral walls themselves, small chilled lead shot was placed under the serosal coat of the stomach. A month after the operation the cats were ready for roentgenographic examination, and records were made on roentgen cinematographic films.

While studying the empty stomach and its various ways of filling, it was first noted that in nine fasting animals with the shot in place, hunger contractions could not be observed. This was not in accord with the evidence of pronounced peristalsis observed when a balloon is inserted into the stomach and inflated, and it suggested that the so-called hunger contractions are caused by distention of the stomach by the recording balloon. In a further similar experiment, after serial roentgenograms were made, shallow peristaltic contractions animating the empty stomach were evident. The theory that food entering the stomach follows closely the lesser curvature, the *Magenstrasse,* was, in the main, disproved. When barium, fluids and food entered the cat's empty stomach, they were carried toward the pylorus by peristaltic waves without following the *Magenstrasse.* This pathway was followed only when small amounts of material entered a stomach already filled with solid food.

In considering the pressure exerted by the gastric walls, it was found that because of active gastric relaxation of the fundus and body of the stomach the intragastric pressure does not change until a large amount of material has been introduced. The rise in pressure which follows further filling is largely the result of stretching of the abdominal walls. Feeding cats large pieces of meat coated with powdered barium enabled Gianturco to follow the physical changes occurring to the foodstuff during digestion and to study the process of liquefaction during the whole course of digestion.

The pyloric mechanism was studied in cats in a similar manner, except that shot was placed also in the walls of the pylorus and duodenum, so that peristaltic waves could be followed on both sides of the sphincter. Although the theory of acid control of the pylorus has been disproved, none of the investigators have ever been able to record simultaneously all the mechanical factors that determine the passage of gastric contents into the duodenum. Cinematographic roentgenograms

7. Gianturco, C.: Some Mechanical Factors of Gastric Physiology, Am. J. Roentgenol. **31**:735 and 745, 1934.

of the prepared cats made it possible to make records of every phase of gastric activity. From these pictures Gianturco concludes that the pylorus responds to approaching waves of peristalsis much as does the adjacent region of the pars pylorica. Food leaves the stomach when the pylorus and the duodenum are relaxed at the same time. Relaxation of the pylorus alone is not followed by the passage of food.

The effect of various foods on the emptying of the stomach was also studied. The various substances fed were mixed with barium, and their course through the stomach was followed with the roentgenoscope. It was found that the emptying time for different foodstuffs depends, first, on the physical state and, second, on the chemical nature of the substance. Fats and hypertonic solutions of salt or sugar were most conspicuous in slowing gastric evacuation, and this action was apparently the result of marked changes in the activity of the walls of the stomach and of the duodenum, which occurred even after removal of the pyloric ring and after gastro-enterostomy.

Quigley [8] commences his article on "Natural Chemical Factors Governing Gastric-Motility" with this statement: "A thorough appreciation of gastro-intestinal physiology is a prime requisite of a gastro-enterologist." Although the motility of the intestine has been ascribed predominantly to nervous mechanisms, actually humoral control may play an important part. The particular problem attacked by the author is how the ingestion of carbohydrates or fats decreases gastric motility and depresses hunger. By means of the balloon method and a series of carefully planned operations on dogs, Quigley showed that these effects are not dependent on the nervous system. In denervated stomachs, fats and sugars led to gastric inhibition similar to that which occurs in normal stomachs. The administration of large doses of secretin and cholecystokinin did not inhibit gastric motility. The motility of the pouch of an entire stomach was not inhibited when fats and carbohydrates were introduced into it; but it was inhibited when fat and carbohydrates were introduced into the duodenum, even when the blood vessels of the stomach had been stripped and phenolized.

Quigley concludes that since nerve reflexes were precluded, the involvement of humoral mechanisms is established. Fats and carbohydrates liberate humoral factors from the mucosa of the upper intestine which resemble an inhibitory hormone. Hunger would terminate, and the inhibition of gastric digestive contractions would retard, the entrance of gastric contents into the duodenum. Such a mechanism might tend to prevent overloading of the stomach and, more especially, the intestine.

8. Quigley, J. P.: Natural Chemical Factors Governing Gastric-Motility, Am. J. Digest. Dis. & Nutrition **1**:425, 1934.

The problem of the mechanism of pyloric function has been the incentive for a long series of investigations, the results of which have been controversial. Cannon's early theory of "the acid control of the pylorus" has been proved incorrect, as Ivy found that strong acids in the duodenum most frequently cause relaxation of the sphincter and regurgitation of duodenal contents into the stomach. Ryle decided that the important factors promoting pathologic hyperacidity are excessive gastric acidity and pyloric hypertonicity. It has long been suggested that gastric acidity in man is controlled by the regurgitation of alkaline duodenal contents into the stomach, but definite proof has been lacking. The importance of the relation of such a mechanism to the high range of acidity usually encountered in cases of peptic ulcer is obvious. Lehrmann and Nelson [9] have utilized a new approach to this problem and have based their observations on a series of cases of duodenal ulcer occurring in man. They modified a Rehfuss tube for gastroduodenal studies by inserting a metal bar dividing the perforated tip horizontally into two parts, which would lie in the stomach. The distal half was connected with a short piece of tubing ending in the usual Rehfuss bulb, which would lie in the duodenum. When the complete gastroduodenal tube was in place (which was always verified by fluoroscopic examination) the pylorus could not close, free regurgitation of duodenal contents could take place into the stomach, and the contents would mix with the gastric secretion. Ordinary fractional analysis of the gastric contents could be carried out by removing specimens through the proximal portion of the tube. It was found that regurgitation of bile and trypsin was very noticeable in all specimens examined during the gastroduodenal tests in 12 cases of duodenal ulcer, although these constituents had been absent in most of the fractional gastric analyses previously made on these patients. Lehrmann's and Nelson's findings lend support to the work of others concerning the dominant part played in gastric function by the pylorus and the duodenum, but of perhaps greater interest to the clinician are the changes in the acid curves noted in these studies. The graphs clearly show that the hyperacidity present on fractional gastric analysis no longer exists during gastroduodenal studies on the same patients when the pylorus is maintained patent. In the latter event the acid curve reaches its peak, approximately a normal figure, within an hour and subsequently drops. Here is convincing proof that free regurgitation of duodenal contents, which is naturally controlled by the tonicity of the pyloric sphincter, plays a part in the "chemical control" of gastric secretion and that pylorospasm is primarily responsible for the hyperacidity so characteristic of peptic ulcer.

9. Lehrmann, W. W., and Nelson, T. M.: The Influence of the Pylorus upon the Regulation of the Acidity of Gastric Secretion, Am. J. Digest. Dis. & Nutrition **1**:245, 1934.

A comparison of intragastric and duodenal factors in lowering the acidity of gastric contents has been made by Wilhelmj, Neigus and Hill.[10] A brief review of the controversial literature on this subject is presented, and a number of experiments on dogs are recorded. The important findings are: 1. Ligation of the bile and pancreatic ducts resulted in slowed and incomplete reduction of acid solutions placed in the stomach. 2. With a free flow of acid in the intact normal stomach, it was possible to separate the secretion into two parts, the first containing unneutralized hydrochloric acid and the second, or extra fluid, composed of neutralized hydrochloric acid and pyloric and regurgitated duodenal secretions. 3. In the whole stomach there was a direct relationship between the amounts of extra fluid, neutral chloride, bile and acid deficit. 4. Pyloric and duodenal secretions reduced acidity more by dilution than by neutralization. The duodenal contents are more efficient in this respect because more are available.

Daikhovsky and Solovei,[11] in a paper entitled "Clinico-Experimental Observations of Excretionary Function of the Stomach," report the excretion time of neutral red in 45 patients with gastro-intestinal disorders. Although a great deal of work has already been done with gastric chromoscopic examination, the authors' observations suggest a new field for this test as a practical medical procedure. They found that the excretory function of the stomach may be upset when there is no disturbance of secretion. From experimentation on animals as well as from an analysis of clinical material, it is evident that the secretion of hydrochloric acid is primarily a function of the mucous membrane of the fundus of the stomach and that the excretion of neutral red is a function of the mucous membrane of the pyloric portion. As these two functions may not correspond, it might be possible to detect pyloric lesions interfering with excretion of the dye even when adequate amounts of free hydrochloric acid were being secreted. Daikhovsky and Solovei found this to be true clinically in the presence of inflammatory changes in the gastric antrum, such as gastritis with or without peptic ulcer and gastroduodenitis, and were able to correlate the chromoscopic findings with changes in the relief of the stomach as determined roentgenologically. They deduce from these observations that retardation or absence of the secretion of neutral red by the gastric mucosa indicates inflammatory changes in the antrum of the stomach and that a test of secretion of neutral red offers a valuable method for the early detection of antral gastritis.

10. Wilhelmj, C. M.; Neigus, I., and Hill, F. C.: Comparison of Intragastric and Duodenal Factors in Lowering Acidity of Gastric Contents, Am. J. Physiol. **107**:490, 1934.

11. Daikhovsky, J. I., and Solovei, M. G.: Clinico-Experimental Observations of Excretory Function of Stomach, Acta med. Scandinav. **83**:79, 1934.

The relationship between many gastro-intestinal disorders and the underlying cause of certain types of anemia is growing closer and closer. A keen student of gastro-enterology must be a close student of hematology. Many of the contributions to these two broad fields of medicine so overlap that any review of gastro-intestinal disorders must reserve a section for recent advances which might be properly placed in either field. A subject which has commanded a great deal of clinical attention and has stimulated an immense amount of experimental work is the relationship of gastric function to anemia. Only a few of the most pertinent articles are reviewed.

Ivy and his co-workers [12] have studied the relationship of gastrectomy to anemia in the dog and the presence of the substances effective in the treatment of pernicious anemia in the canine stomach and liver. Dogs deprived of their stomachs do not show the blood picture of pernicious anemia but rather that of hypochromic anemia, which responds to suitable iron therapy and does not respond to the administration of the liver extract fraction G from a patient with primary anemia. Rats and pigs on which gastrectomy has been performed show the same form of anemia. The primary defect seems to be one of absorption of iron. Canine desiccated stomach and canine liver are effective in the treatment of pernicious anemia in man but are of low potency in comparison to bovine stomach and liver. These observations lead the authors to question whether a lack of the intrinsic gastric factor of Castle can be the primary cause of pernicious anemia. They suggest that this unknown substance may also be present in the intestine, or that other factors are concerned in the etiology of this disorder.

Although macrocytic anemia resembling pernicious anemia has not been constantly produced in dogs and swine and in man by gastrectomy, Miller and Rhoads [13] produced this type of anemia in swine given a deficient diet. A characteristic symptom complex developed with a diet which causes canine black tongue and which is deficient in those antianemic factors which are necessary to the successful treatment of pernicious anemia. Macrocytic anemia, lesions of the oral mucous membranes, gastric achlorhydria, diarrhea and motor weakness of the extremities were the principal manifestations. Changes in the bone marrow characteristic of pernicious anemia also occurred. When the disease was present, it was impossible to demonstrate hematopoietic activity of the gastric secretion or liver when tested on human beings

12. Ivy, A. C.; Richter, O.; Meyer, A. F., and Greengard, H.: Relation of Gastrectomy to Anemia; Presence of Substances Effective in Pernicious Anemia in Canine Stomach and Liver, Am. J. Digest. Dis. & Nutrition **1**:116, 1934.

13. Miller, D. K., and Rhoads, C. P.: The Experimental Production of Loss of Hematopoietic Elements of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia, J. Clin. Investigation **14**:153, 1935.

with pernicious anemia. The macrocytic anemia in swine responded to liver therapy just as in human patients. Miller and Rhoads are the first to produce a syndrome of pernicious anemia in experimental animals, and it is noteworthy that it was accomplished by dietary measures and that the gastric achlorhydria occurred secondarily.

Dedichen [14] has studied the changes of the blood in 164 patients who had previously been subjected to gastric resection. Anemia developed in just over 50 per cent, which is a higher incidence than occurs in "spontaneous" achylia. Only 27 per cent of the men were affected, while 82 per cent of the women became anemic. All but 1 of 34 women under 40 were anemic. In most cases the anemia was of the secondary type, with a low color index, but the cases of 2 patients with the characteristics of pernicious anemia are described in detail. The author believes that achylia cannot be solely responsible for the changes of the blood, particularly since some of his patients with anemia showed free hydrochloric acid despite gastric resection.

Larsen [15] has also studied the blood of a group of patients on whom gastrectomy had been performed and, in addition, patients on whom gastro-enterostomy had been performed. The chief value of his report is that his observations were made on an average of about twelve and one-half years after the operation. Of 35 women whose stomachs had been resected, he found 17 with anemia (hemoglobin content less than 80), and of 51 men, 14 had anemia (hemoglobin content less than 90). Of 26 women on whom gastro-enterostomy had been performed, 9 had anemia. Only 10 men of the group of 39 had anemia following the same operation. Only 1 case of typical pernicious anemia was noted, despite the long postoperative period. Larsen's figures correspond to the majority reported in the literature and are similar to those of Dedichen.

Gastritis.—The question of gastritis is receiving a great deal of attention and is mentioned elsewhere in this review in intimate connection with other subjects. Most of the recent studies are recorded in the foreign literature; they have been largely advanced clinically by the introduction of a flexible gastroscope and by the development of a special technic in examining the gastric mucosa roentgenologically. Although a good deal of new and stimulating information has been presented, these highly specialized methods of studying a patient with a stomachache are not yet available to the average internist or even to the clinic of the average hospital. One is almost led to believe that a superroentgenologist on the right hand and a gastroscope in the left

14. Dedichen, J.: On Blood-Changes After Gastric Resection, Acta chir. Scandinav. **75**:242, 1934.

15. Larsen, T. H.: On Presence of Anemia After Ventricle Operations, Acta med. Scandinav. **83**:110, 1934.

hand are necessary additions to the investigation of gastric disorders. Undoubtedly for practical purposes these specialized investigations are required in a small number of cases; just how small a number remains to be seen. It is possible that certain severe forms of gastritis are not as common in the United States as abroad, just as large indurated gastric ulcers are not as common here. Of particular interest as regards the study of gastric inflammation is the increasing mass of evidence gathered from different sources that gastritis, often termed antral gastritis, precedes the formation of peptic ulcers of the stomach.

The most complete and up-to-date description of gastritis is given in Henning's book on inflammation of the stomach, published in Germany. It is reviewed by Kalk.[16] All forms of acute and chronic gastritis are discussed in detail and in the light of the most recently acquired knowledge made available by roentgen and gastroscopic examination. The importance of the gastroscope is strongly emphasized, and every phase of its usefulness is described. Practically everything worth knowing on the subject is made available in Henning's excellent work.

Henning discusses the problem of gastritis more briefly, though thoroughly, in the *Medizinische Klinik*.[17] The known etiologic causes of inflammation of the stomach are mechanical and chemical injuries to the mucous membrane, outspoken infections and possibly occult infections. There is much to suggest peptic digestion as a primary cause, but this is not yet completely proved in man. The symptoms are not necessarily specific, but pain similar to that of the pyloric syndrome is common and may resemble that of peptic ulcer of short duration. In many cases of severe gastritis the condition cannot be diagnosed by roentgen examination, and only gastroscopic study will give conclusive evidence of inflammation. Gastric analysis usually reveals diminished acidity, and excessive amounts of mucus may or may not be present. The *Trockendiagnostik* (to be described later) is a simple and valuable diagnostic aid.

In many cases the condition clears up when the underlying cause is relieved, such as circulatory failure and known infectious diseases. In cases of doubtful etiology it is most important to remove any focus of infection. In the many cases of unproved etiology, symptomatic therapy must be instituted. Details of gastric lavage, the administration of drugs, substitution therapy, such as the administration of dilute hydrochloric acid, pepsin and mucin and a dietary regimen are all presented in a practical manner. Many patients rapidly improve on such a regimen. Roentgenologic and endoscopic examination should not be delayed in chronic cases but must be carried out by specialists.

16. Kalk, H.: Gastritis, Deutsche med. Wchnschr. **60**:236 and 276, 1934.

17. Henning, N.: Ueber Gastritisprobleme, Med. Klin. **30**:1151, 1934.

Observations of a dried drop of gastric juice have been made to distinguish between the secretion of a normal stomach and the secretion of an inflamed stomach. The drop from a stomach with gastritis shows a peripheral transparent laked area at the circumference, which has been termed the *Ringphänomen,* which does not normally appear and is caused by the increased protein content of the gastric secretion. Henning and Norpoth [18] have carried on further experimental observations on the microscopic picture of dry gastric juice.

The dry residuum of a drop of pure gastric secretion shows a lattice work pattern of crystals of sodium chloride, which differs in its appearance when saliva or duodenal contents are added. These changes are well illustrated, and the characteristics of pure gastric juice are quite different from mixtures with other secretions. Henning and Norpoth also added small amounts of blood serum to a drop of pure gastric juice, producing the clear Ring zone which is characteristic of increased protein concentration.

One of the first reports on the use of the new Wolf-Schindler flexible gastroscope in this country is by Benedict,[19] working at the Massachusetts General Hospital. In his introduction he states that the first gastroscopic examination was performed in 1868 by Küssmaul, whose subject was a professional sword swallower. Most of Benedict's 75 patients "did not find gastroscopy a severe ordeal; in fact, one patient slept throughout the examination." The author believes that direct inspection of the mucous membrane of the stomach is a valuable adjunct to roentgen studies in the diagnosis of gastric disorders. The lining of a normal stomach is described and illustrated before Benedict passes on to the findings in the stomachs of persons with gastritis. The stomachs of 22 patients with inflammation of the wall of the stomach were observed, and redness, swelling, tortuous rugae and, in some cases, erosions and small hemorrhages were readily discerned. Edematous areas, with collections of mucopurulent material characteristic of hypertrophic gastritis, were seen. Histories of cases in which gastroscopic study was of paramount importance in establishing a correct diagnosis are included, and the history of the simulation of ulcer by gastritis is emphasized. Gastric ulcer is easily visualized; and the course of healing is followed even more accurately by gastroscopic study than by roentgen examination. At times, a benign ulcer may be distinguished from a malignant ulcer on its appearance alone. There were no cases of gastrojejunal ulcer in this series. In 2 of 12 cases of gastric tumor the

18. Henning, N., and Norpoth, L.: Experimentelle Untersuchungen über das microskopische Bild des eingetrockneten Magensaftes, Arch. f. Verdauungskr. **55**: 35, 1934.

19. Benedict, E. B.: Examination of the Stomach by Means of a Flexible Gastroscope: A Preliminary Report, New England J. Med. **210**:669, 1934.

tumor was overlooked on gastroscopic examination but in another case a tumor was observed which was not found on roentgen examination.

The author concludes that examination by means of the flexible gastroscope is an easy, harmless and profitable procedure. The greatest field of usefulness is in cases of gastritis, but it is also useful as an adjunct to roentgen study of other conditions.

Peptic Ulcer.—Hanke [20] has studied the experimental production of acute gastric ulcers in cats by means of repeated injections of insulin. He administered a series of doses until the animal died, usually within thirteen hours, with signs of hypoglycemic shock similar to those occurring in man. No constant observations as regards gastric motility were made post mortem, although in most instances the pylorus was markedly contracted and the cardia relaxed. The gastric secretion was significantly increased and was high in acid content. Grossly and microscopically the stomachs showed the formation of acute ulcers and erosions, which extended into the lower end of the esophagus and into the upper portion of the duodenum. The mucous membrane was markedly inflamed, especially in the pyloric region, the epithelial surface being extensively involved, with definite extension into the deeper layers. Hanke has termed the condition acute hormonal gastritis, comparable to that found in similar experiments using morphine, pilocarpine and caffeine instead of insulin.

The interpretation of these results is that the hormone insulin stimulates an extensive secretion of gastric juice rich in acid and pepsin and that gastritis is a result of their surface digestive action. This process goes on to areas of fibrinous necrosis with acute inflammatory leukocytic infiltrations. Such a "peptic gastritis" may be an early stage in the formation of peptic ulcer in man. Toxins and pyloric spasm may predispose to a similar form of gastritis.

Gastric ulcers associated with cinchophen poisoning were unknown before 1932. In that year a typical chronic ulcer of the stomach and duodenum developed in a number of dogs receiving large doses of this drug. In the same year a case was reported in man. Block and Rosenberg [21] report the second case and consider the possible etiologic relationship. The chronic gastric ulcers of their patient were unusual in their irregular oval formation and in their location at the cardia. The patient had taken mono-iodocinchophen on and off for three years, during which time gastro-intestinal symptoms developed. She died shortly after profuse hematemesis.

20. Hanke, H.: Experimentelle Untersuchungen über hormonale Ulcuserzeugung; die akute erosive Insulin-gastritis und ihre Pathogenese, Ztschr. f. d. ges. exper. Med. **94**:405, 1934.

21. Block, L., and Rosenberg, D. H.: Gastric Ulcers Associated with Cinchophen Poisoning, Am. J. Digest. Dis. & Nutrition **1**:29, 1934.

A number of papers have appeared on recently introduced methods of medical treatment of chronic peptic ulcer of the stomach and duodenum. This search for better methods of therapy in this field not only denotes a sustained interest in the problem but suggests that the generally utilized dietary and alkali management developed in the early part of this century is not altogether satisfactory. A few of the newer methods of treatment are based on sound physiologic principles; many seem to be based more on theory than on fact. For the sake of completeness all have been more or less briefly reviewed. It does not appear that any of them will replace the long established Sippy type of regimen, but some of them may prove a helpful adjunct to this form of therapy, and some may prove valuable in cases in which the condition is otherwise refractive.

Treatment of peptic ulcer with gastric mucin was first reported five years ago and has been widely taken up since. The clinical results in 555 cases studied by questionnaires issued by the Gastric Mucin Committee of the Northwestern University Medical School have been published by Fogelson.[22] The gastric mucin dispensed for treatment has had to meet rigid requirements of standardization by the committee since 1931. The conclusions are: 1. Of 494 patients with peptic ulcer treated throughout the United States, all symptoms were controlled in 70.5 per cent, partial relief was obtained in 23 per cent, and failure occurred in 6.5 per cent. 2. Of 217 patients with intractable ulcers, 69 of whom had submitted to previous surgical procedures, gastric mucin afforded complete relief in 63.1 per cent, partial relief in 29.4 per cent and no relief in 7.5 per cent. 3. The results in this group of patients with intractable ulcer suggest the possibility of obtaining symptomatic relief with gastric mucin when accepted orthodox measures have failed. 4. The permanence of the results is not considered, because of the limited period of observation.

The use of mucin in the treatment of peptic ulcer has stimulated a series of investigations into the properties of this substance which would justify its clinical use on a sound physiologic basis. In a number of carefully controlled experiments on the effect of mucin and mucinoids on peptic digestion, Bradley and Hodges[23] found the action of mucin to be equivalent to reducing the concentration of active enzyme. The inhibition is one of rate only. Their experiments indicated a temporary delay in the digestive removal of fibrin covered by gastric mucin and by okra. This would appear to be of real significance in preventing interruption of the healing process.

22. Fogelson, S. J.: Gastric Mucin Treatment for Peptic Ulcer: Report Based on Questionnaires, Arch. Int. Med. **55**:7 (Jan.) 1935.

23. Bradley, H. C., and Hodges, M.: Effect of Mucin and Mucinoids on Peptic Digestion, J. Lab. & Clin. Med. **20**:165, 1934.

In the latter part of 1933 Meyer, Seidmon and Necheles [24] reported on the treatment of seventeen patients with ulcer with a preparation of powdered okra. Fourteen noted immediate relief, which was all the more striking as no other forms of treatment were employed.

If the work of these authors is substantiated, the patient's choice between the vegetable mucin of okra, so commonly associated with chicken soup, and the mucin secretion of the hog's stomach would not be difficult to anticipate.

Bulmer [25] reports the results in 52 unselected cases of peptic ulcer in which the condition was treated by the parenteral injection of histidine, one of the amino-acids. This study was undertaken because Aron and Weiss had shown that the formation of experimental ulcers in dogs could be prevented by injections of histidine and because excellent relief of symptoms was obtained in 17 cases in which peptic ulcer was so treated. So far as possible Bulmer used histidine. His immediate results showed symptomatic cure in 58 per cent of the cases and failure in 23 per cent. In a follow-up study, 3 patients were found to have a relapse. Gastric ulcers seemed more amenable to treatment than duodenal ulcers. Patients with a short history responded better than those with a long history. The author states that no final conclusions have been drawn but that he believes that the results are better and quicker than those of the more orthodox methods.

During a six year period at the Wurzburg Clinic, Engel [26] studied the effects of foreign protein therapy in cases of gastric and duodenal ulcer. He administered a plant albumin intravenously in a selected group of 70 cases in which there had been no response to the ordinary dietary regimen. A few patients had chills, fever and vomiting. Fifty-eight per cent of the patients became symptom-free, 30 per cent were improved and only 12 per cent remained completely unchanged. Engel considers these results very favorable and states that all patients with an uncomplicated ulcer which does not respond properly to diet should have a course of foreign protein therapy before surgical intervention is considered.

Foreign protein therapy in the treatment of peptic ulcer has been popular abroad but has received little attention in the United States. Cunha [27] reports his experiences with the use of a proprietary prepa-

24. Meyer, J.; Seidmon, E. E., and Necheles, H.: Treatment of Peptic Ulcer with Powdered Okra, Illinois M. J. **64**:339, 1933.

25. Bulmer, E.: Treatment of Peptic Ulcer, with Note on Fifty-Two Cases, Lancet **2**:1276, 1934.

26. Engel, A.: Beitrag zur Kenntnis der Erfolge der "Proteinkörpertherapie" bei Magen- und Duodenalulcus, Arch. f. Verdauungskr. **56**:256, 1934.

27. Cunha, F.: Experiences with New Mode of Treating Peptic Ulcer, Am. J. Surg. **23**:219, 1934.

ration containing lipoproteins and emetine. Cunha states that the lipoprotein has a tendency to decrease gastric peristalsis, arrest pylorospasm and promote healing of the local lesion. Emetine relaxes smooth muscle and has antibacterial properties. Fifty-one patients were completely examined and carefully followed. In 29 cases treatment had been completed a year previous to the report. Each patient received 1 ampule of the aforementioned solution intravenously every fourth day for ten doses. No reaction appeared. A dietary regimen was followed for four weeks. In all but 2 patients complete relief from pain occurred promptly, and healing of the ulcer was promoted, as noted by roentgen examinations. Reports of 8 cases, with roentgenograms, are included to emphasize the benefits of protein therapy and to prove that the patients could continue their daily routine while under treatment.

Sandweiss and Meyers [28] have tried bacterial vaccines as a form of foreign protein therapy in cases of peptic ulcer. They used a mixed respiratory vaccine in 33 cases of intractable ulcer and treated patients in a total of forty-eight attacks. Remission occurred in 70.9 per cent, but in about one half of these symptoms reappeared in less than three months. Only 1 patient was symptom-free thirty-six months later. A second course of treatment was likely to give either relief for only a short period or no relief. The authors believe that the chief value of this form of foreign protein treatment rests in its capacity for initiating remissions and that cure should not be expected.

Glaessner [29] has long advocated an original conception of the cause of peptic ulcer on which he has based his "specific therapy." The normal balance between the pepsin of the gastric secretion and the antipepsin of the wall of the stomach is upset, with a definite diminution in antipepsin and the resultant digestion of the gastric mucosa and formation of ulcer. The parenteral injection of pepsin will stimulate the formation of antipepsin in the stomach, restore this balance and promote healing of the lesion.

In treating about 1,000 patients with peptic ulcer of the stomach and duodenum Glaessner injected a sterile neutral solution of pepsin which produces only a slight reaction. A special dietary regimen was included as a part of the therapy. Excellent results were obtained in about 50 per cent of this large series, and another series is cited in which good results were obtained in 90 per cent. It is impossible to evaluate the exact benefits, if any, of this pepsin therapy from the data presented in the report.

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28. Sandweiss, D. J., and Meyers, S. G.: Treatment of Peptic Ulcer with Bacterial Vaccines (Foreign Protein), Am. J. Digest. Dis. & Nutrition **1**:338, 1934.

29. Glaessner, K.: Organotherapie des Ulcus pepticum, Wien. klin. Wchnschr. **47**:513, 1934.

Einsel, Adams and Myers [30] have contributed a report on aluminum hydroxide in the treatment of peptic ulcer. In colloidal form it reduces the emptying time of the stomach, lowers gastric acidity and is devoid of deleterious side-effects. With its power of fixing large quantities of hydrochloric acid, it has the advantages of treatment with alkali without the disadvantages of absorbable alkali, and there is no subsequent stimulation to the production of free acid, as with the use of bicarbonate of soda. Several charts are presented illustrating the lowering of gastric acidity by the regular administration of gelatinous aluminum hydroxide. It is pointed out that acidity again increases when alkali therapy is discontinued.

Jones [31] discusses the use of insulin in the treatment of peptic ulcer. The rationale of this form of therapy is apparently largely based on the author's familiarity with pertinent investigations in some of the Russian clinics. He states that insulin increases the secretion of the stomach, which assumes an inert type, and that insulin has the properties of a powerful alkalizer. There is a lowering of vagotonus, thus removing the manifestations of spasmophilia. Jones treated 26 ambulatory patients, injecting, on the average, from 20 to 30 units of insulin daily. They were allowed their customary food and were required to take 100 Gm. of mashed potatoes at each of two main meals. Of the 12 patients with "fresh" peptic ulcer, all but 1 were symptom-free within ten days. All gained weight. After from ten to fifteen days, roentgen examination revealed no definite signs of ulcer. Equally good results were attained in 6 cases of recurrent ulcer. Satisfactory improvement with partial relief from pain and gain in weight and well-being occurred in the 8 cases complicated by perigastritis and adhesions. In some cases the ulcer had been recalcitrant to other forms of treatment. The author noted a change from the vagotonic type of stomach to normotonus and also an increase in gastric secretion with a corresponding improvement in appetite; at the same time there was a decrease in gastric acidity.

All the cases of ulcer which have been studied at the Peter Bent Brigham Hospital during the nineteen years of its existence have been studied as regards the results of treatment, which has been some type of Sippy regimen or some form of surgical procedure. Of a total of 1,435 cases, Emery [32] has analyzed 1,253. Nearly all of these have been followed over one year, and 333 were followed for six years or longer.

30. Einsel, I. H.; Adams, W. L., and Myers, V. C.: Aluminum Hydroxide Treatment of Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **1**:513, 1934.

31. Jones, C. R.: Insulin in the Treatment of Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **1**:135, 1934.

32. Emery, E. S.: The Treatment of Peptic Ulcer Based on One Thousand, Four Hundred and Thirty-Five Cases, Am. J. Digest. Dis. & Nutrition **1**:520, 1934.

A striking feature is the small number of cases in which there was complete relief of symptoms. Only 13.7 per cent of the patients receiving medical treatment and 19 per cent of the patients receiving surgical treatment were relieved, while 23.8 per cent of the patients who received no treatment were symptom-free after leaving the hospital. On the other hand, almost half the untreated patients remained unimproved. A table shows the percentage of "satisfactory results" for all types of treatment. A study of this table reveals the fact that medical treatment resulted in a higher percentage of satisfactory results than the surgical methods and that the complete Sippy regimen was 90 per cent satisfactory. Too much attention is paid to the healing of the ulcer and not enough to preventing a relapse after healing has taken place. Emery found the causes of relapses, in the order of their greatest frequency, to be fatigue, emotional disturbances and recurrence of infection. In only 37 cases were dietary indiscretions mentioned as a cause of relapse.

The results of surgery and of medicine in uncomplicated cases are similar. Obstruction was better relieved by surgical intervention. Neither form of therapy was superior to the other in the prevention of bleeding, although surgical procedure will prevent further hemorrhage in a number of cases in which bleeding persists. The height of gastric acidity does not influence the outcome of treatment, but nearly all patients with high acidity who fail to improve have hypersecretion. In these patients jejunal ulcers invariably develop after surgical intervention.

Emery's analysis of the results of treatment in cases of peptic ulcer is not unlike many others which appear every year. It has been included primarily for a basis of comparison with the preceding forms of medical treatment, as it well represents the efficacy of the types of therapy which have thus far survived the test of time.

There is an increasing appreciation of the fact that many patients with ulcer must have continuous treatment, like patients with diabetes or pernicious anemia, and that individualization is necessary in the supervision of each case.

Rachet [33] has made an extensive medical survey of ulcer following gastro-enterostomy. He has considered the immediate and late postoperative treatment and the intestinal disturbances which may develop after such an operation. He concludes that the complications encountered after gastro-enterostomy may be due to the evolution of an ulcer which has persisted despite the operation or may be due to the gastro-enterostomy itself, in that a new gastro-intestinal physiology has been created to which the organism is not adapted. To prevent accidents

33. Rachet, J.: La surveillance médicale des ulcéreux après la gastro-entérostomie, Bull. gén. de thérap. **185**:132, 1934.

and to ameliorate the complications is the rôle of medicine after surgical intervention. There is no better example of the necessity for cooperation between the internist and the surgeon than the after-care of patients on whom a gastro-enterostomy has been performed.

In an article on the "Conservative Treatment of Ulcer of the Stomach and Duodenum" Judd and Waldron [34] present their views on the most satisfactory methods for surgical control of these lesions. A brief and interesting historical background leads up to a steady undertone of conservatism. The illustrations are profuse and instructive. The authors conclude that the results of excision and gastrojejunostomy amply justify this procedure for gastric ulcer. Several methods of treatment of duodenal ulcer are now available, if properly applied. Gastrojejunostomy, removal of the duodenal lesion with or without excision of part of the pyloric musculature and gastroduodenostomy without removal of the lesion may each be appropriate. There seems to be no good reason for radical resection for duodenal ulcer.

Gastric Neoplasms.—Shay and Schloss,[35] because of a case of gastric carcinoma of unusual interest, consider the gastric ulcer-cancer problem with great care and thoroughness. After weighing the evidence for and against the theories of several moot questions they conclude: 1. Gastric ulcer is only infrequently a precursor of a malignant gastric process. 2. From the duration and nature of the symptoms of ulceration of the stomach and from the response to therapy, it cannot be positively stated that the lesion is benign or malignant in any given case. 3. Although gastric anacidity is common in cases of cancer of the stomach, free acid or a normal or high acid content is seen in almost as many cases. 4. The incidence of those cases of carcinoma in which adequate free hydrochloric acid is present is entirely too high to be accounted for by the ulcer-cancer group. 5. Anacidity in cases of gastric cancer is best accounted for by preceding or associated chronic gastritis. 6. Given an ulcerating gastric lesion, anacidity is presumptive evidence in favor of carcinoma, but the presence of normal or increased acidity is of little, if any, value in militating against a malignant process. 7. Roentgenograms are of little help in the present problem.

The case of Shay and Schloss is placed on record because a physician with as wide experience in gastro-enterology as A. F. Hurst stated that he had never observed a case of gastric carcinoma in which free hydrochloric acid was present at an early stage and disappeared as the

34. Judd, E. S., and Waldron, G. W.: Conservative Surgical Treatment of Ulcer of the Stomach and Duodenum, Am. J. Digest. Dis. & Nutrition **1**:262, 1934.

35. Shay, H., and Schloss, E. M.: Consideration of Gastric Ulcer-Cancer Problem, with Report of Case of Ulcerating Carcinoma in Which Gastric Acidity Changed from Normal to Anacidity While Under Observation, Ann. Int. Med. **7**:1218, 1934.

disease advanced. Such a change in gastric acidity did occur in the authors' patient, and a series of four fractional gastric analyses are recorded which illustrate the diminution and ultimate disappearance of free hydrochloric acid during the progress of a carcinomatous ulcer.

Bishop [36] reports an additional case of cancer of the stomach in the literature on the occurrence of this neoplasm in young persons. Gastric carcinoma is very uncommon in the second decade of life. Bishop's patient was a girl aged 16, who had no gastric symptoms. In view of marked anemia, the enlargement of the lymph glands and a diagnosis of Hodgkin's disease based on a biopsy, the correct diagnosis was not made during life. The anatomic diagnosis was carcinoma of the stomach with extensive metastases, including large masses in both ovaries.

In a case reported in a paper entitled "Total Gastrectomy for Cancer with After Examinations of the Absorptive Capacity of the Intestine," Bull and Stang [37] noted an increased amount of protein and fat in the stool. The fat content was the more marked, but the patient had been on a diet relatively rich in fats. The esophagus and small intestine appeared normal on roentgen examination. A year after operation the patient was carrying on his regular work and taking a liberal diet. He had no discomfort from food as long as he avoided large meals.

Dahlgren [38] reports an additional case of endothelioma of the stomach which differs considerably from the 11 cases already recorded in the literature. Usually this tumor is endogastric, arising within the stomach, and is not large. Metastases may occur, although in the 6 cases in which operation was performed none were found. The tumor described in detail by the author was exogastric, was large, weighing 2 Kg., and was of benign endotheliomatous nature. The final histologic diagnosis was lymphangio-endothelioma.

DUODENUM

In a discussion on duodenitis and its roentgenologic characteristics, Kirklin [39] brings this subject up to date and emphasizes certain features at operation. The lesion in duodenitis is to be distinguished from duodenal ulcer by the lack of formation of a crater and lack of induration, although both show hyperemia and stippling of the serosa. It may occur

36. Bishop, E. L.: Cancer of Stomach in Young Patients, Am. J. Cancer **20**:807, 1934.

37. Bull, P., and Stang, J.: Total Gastrectomy for Cancer with After-Examinations of the Absorptive Capacity of the Intestine, Acta chir. Scandinav. **75**:319, 1934.

38. Dahlgren, L.: Endothelioma of the Stomach, Acta chir. Scandinav. **75**: 451, 1934.

39. Kirklin, B. R.: Duodenitis and Its Roentgenologic Characteristics, Am. J. Roentgenol. **31**:581, 1934.

independently or in association with true ulcer. From the point of view of histologic changes, the relation between duodenitis and duodenal ulcer has not been conclusively determined, although it is evident that at times the first precedes the second. It is desirable to distinguish between these lesions, if possible, in order to select appropriate therapeutic measures.

Clinically, a definite differentiation of these two disorders is not possible, although in duodenitis the symptoms are less severe, are more irregular and are less readily relieved by food and alkalis. In considering the roentgenologic aspects, 32 cases in which operation had been performed and the pathologic diagnosis established by microscopic examination of excised tissue were selected for analysis; the coincidence of peptic ulcer could be rigidly excluded. The first characteristic of duodenitis is hyperirritability of the duodenum, typically manifested in intense spasticity and hypermotility. The bulb is small and deformed, and the configuration of the deformity varies rapidly from moment to moment. The bulbar shadow lacks density, and the shadows are hazy. A second characteristic is the coarsely and irregularly reticular mucosal pattern. A third is the absence of a crater, and the fourth is the absence of gastric retention or other evidence of obstruction. A small hypertonic active stomach completes the typical roentgenologic syndrome of duodenitis. In only one fourth of the cases were the roentgen signs so pronounced that a definite diagnosis was obvious. In 20 of the 32 cases a diagnosis of duodenal ulcer was made, probably because of the deformity of the duodenal bulb, which has long been recognized as a reliable sign of duodenal ulcer.

An extensive study of the clinical significance of duodenal diverticula has been made in Morawitz's clinic in Leipzig. Lemmel's observations [40] are based on 50 cases occurring among 3,324 patients, on whom roentgen studies of the gastro-intestinal tract were made. In a discussion of the frequency of duodenal diverticula, a table of 9 different autopsy reports is presented in which the incidence varies between 0.5 and 16.2 per cent. Lemmel explains this extraordinary variation as being due to a lack of careful examination on the part of some pathologists. A second table shows the incidence as revealed by roentgen examination to lie between 0.4 and 5.2 per cent. The author's own large series shows the presence of diverticula in 1.5 per cent of cases. The technic of examination is again blamed for the lack of uniformity of incidence. A third table presents the incidence of duodenal diverticula in relation to age groups. The increased percentage of cases with advancing years is striking. It rises from 0.5 per cent at from 30 to 49 years to 2.6 per cent at

40. Lemmel, G.: Die klinische Bedeutung der Duodenaldivertikel, Arch. f. Verdauungskr. **56**:59, 1934.

from 50 to 69 years, reaching a peak of 9.7 per cent at from 70 to 90 years. It may be stated that 10 per cent of the patients over 70 have the lesion. Its incidence is compared to the frequency of gastric and duodenal ulcer and to gastric cancer. It is much more common than peptic ulcer and almost as common as cancer in the advanced age group.

Contrary to a number of observers, Lemmel states that the majority of duodenal diverticula cause symptoms either directly or indirectly. Gastro-intestinal disturbances and signs of inflammation cannot be clinically localized by any definite symptom complex. The indirect symptoms are due to secondary involvement of the pancreas, bile passages and liver. The presence of cirrhosis of the liver was proved in 10 per cent of Lemmel's cases. In cases of clinically recognized chronic pancreatitis, a diverticulum is often the determining cause. It is the commonest cause of disease in the region of the ampulla of Vater next to cancer and gallstones.

A clinical diagnosis of duodenal diverticulum is possible but must be confirmed by roentgen examination. The cause of the lesion is not congenital but an acquired pulsion diverticulum of old persons and may be compared to hernia elsewhere. Therapeutically, if the diverticulum is producing pressure symptoms in the neighborhood, it must be extirpated or the duodenum resected.

Ettinger and Davis[41] emphasized the importance of the refined compression technic devised by Ackerlund and Berg in the roentgen diagnosis of activity and cure of duodenal ulcer. Few reports of this method of examination have appeared in the American journals. It requires time and skill but will demonstrate the actual anatomic change, namely, the ulcer, with the highest possible detail and nearly as the pathologist sees it. Ettinger and Davis were able to demonstrate the niche in 50 per cent of 48 cases of duodenal ulcer, including instances in which there was no deformity of the cap. When deformity of the cap alone is the basis of diagnosis, as is so often the circumstance, no information can be obtained as to the activity of the lesion. Although clinical symptoms usually clear up quickly after therapy is instituted, roentgen examination six weeks later reveals over half the ulcers unchanged in size. Complete healing finally occurs, as may be demonstrated by roentgen study six months later in a control examination. While certain technical factors may be disturbing in visualization of the niche, the authors think another factor must be considered, namely, gastritis, which practically always accompanies ulcer.

By using the compression technic the roentgenologist can demonstrate the niche in a large percentage of cases of duodenal ulcer and

41. Ettinger, A., and Davis, W. E.: X-Ray Diagnosis of Activity and Cure of Duodenal Ulcer, Am. J. Digest. Dis. & Nutrition **1**:579, 1934.

thereby play a valuable part in determining the degree of activity. Some excellent illustrative figures accompany this article which are well worth seeing.

Carcinoma of the duodenum is rare. Two cases have been added to the literature by Lisa, Levine and Fitzhugh.[42] The reports are concise, and illustrations of the pathologic specimens are included. In 1 case the location was periampullary, and jaundice appeared. The other was supra-ampullary, and intense vomiting was present, said to be characteristic of cancer at this site.

Another report of a case of primary cancer of the duodenum brings out some valuable facts. When the patient first came under observation he complained of weakness and vague symptoms in the upper part of the abdomen of three months' duration. Examination revealed anemia and blood in the stools. The gastro-intestinal roentgen study was negative but showed an obvious alteration of mucosal pattern corresponding to the site of lesion proved later. The patient was admitted to the hospital a year later, having had jaundice for two weeks. Roentgen study revealed a filling defect in the second portion of the duodenum, with indications of rigidity of the wall of the intestine in this same area. A cholecystostomy was performed, but the patient died three days later. Necropsy showed the growth to be periampullary, occurring at the commonest site of primary cancer of the duodenum.

Swenson and Levin [43] report this case primarily because of the unusual roentgen findings, which might have suggested the correct diagnosis at the first examination. It is difficult to visualize the entire duodenum, and consequently such lesions are all too readily overlooked. This was of particular importance in this case as no metastases were found at autopsy, suggesting that complete excision might have been carried out at the time of the original study and the life of the patient saved.

SMALL INTESTINE

Bickel and Wagner [44] carried out a long series of observations on intestinal secretion in a woman with a Thiry fistula of the ileum in an endeavor to study the mechanism involved in the production of the secretion and its relation to conditioned and unconditioned reflexes. They compared their findings to those on dogs studied in a similar

42. Lisa, J. R.; Levine, J., and Fitzhugh, W. M.: Primary Carcinoma of Duodenum, J. Lab. & Clin. Med. **20**:150, 1934.

43. Swenson, P. C., and Levin, A. G.: Primary Carcinoma of Duodenum: Case Report, Am. J. Roentgenol. **31**:204, 1934.

44. Bickel, A., and Wagner, H. I.: Der Mechanismus der Dünndarmsekretion beim Menschen und seine Verknüpfung mit der psycho-physiologischen Sphäre auf dem Wege über "addierte Reflexe," Arch. f. Verdauungskr. **55**:53, 1934.

manner. As the mechanism of intestinal secretion is partly a nervous reflex and partly humorochemical, they considered a mechanical or chemical stimulation of the mucous membrane—which locally excited the intestinal glands to secrete—to represent an unconditioned reflex. Although this seemed to be the only type of reflex in dogs, there is also set up in man a conditioned reflex under the control of the cerebrum, a psychophysiologic process. The existence of such a conditioned reflex is of great significance in the understanding of the secretory neuroses of the intestine.

Alcoholic drinks, amino-acids, a mixed diet and diets rich in protein and in fat produce a more copious secretion from the intestinal glands than carbohydrate nourishment or a fare of green vegetables. The same chemical excitant can produce both a conditioned and an unconditioned reflex, resulting in secretory activity of the intestinal glands. This the authors demonstrated by introducing amino-acid solutions locally through the opening of the fistula into the isolated intestine and in another experiment by mouth. In each experiment active secretion of intestinal juice was noted within a few minutes.

It was found that powdered pancreas strongly stimulates the intestinal glands. Their activity is intermittent, and on the injection of nourishment there is an intermittent period of at least two minutes before intestinal secretion commences. Bickel and Wagner emphasize also that the lack of the unconditioned reflex in dogs may account for many of the discrepancies in trying to apply the results of experiments on intestinal secretion in animals to clinical observations in man.

A critical review of the recent literature on diverticulosis of the small intestine is presented by Chapman.[45] He was able to discover reports on only 32 typical cases. They are discussed and analyzed. A hitherto unreported case of his own is described. An old man with a psychosis had been under observation in the hospital about two months. No noteworthy gastro-intestinal symptoms were observed. He died after a fall. About 3 or 4 feet (91 to 121 cm.) of the jejunum showed a great number of diverticula opening outward at the mesenteric attachment. The size of the evaginations varied from hardly discernible diverticula to some as large as 4 cm. in diameter.

Schmidt and Guttman,[46] in an article entitled "Multiple Diverticula of the Jejunum and Duodenum Simulating Gastric Diverticula and Complicated by Cholelithiasis," present a most instructive case and discussion

45. Chapman, J.: Report of Case of Diverticulosis of Small Intestine with Critical Review of Recent Literature, Ann. Int. Med. **7**:1376, 1934.

46. Schmidt, E. A., and Guttman, P. H.: Multiple Diverticula of Jejunum and Duodenum Simulating Gastric Diverticula and Complicated by Cholelithiasis, Am. J. Roentgenol. **31**:200, 1934.

of jejunal diverticula. Their patient had a laparotomy with removal of the appendix and gallbladder six weeks previously elsewhere, but serious gastro-intestinal symptoms persisted. The roentgen diagnosis after an incomplete examination owing to the patient's poor condition was duodenojejunal diverticulosis. As vomiting persisted, another operation was attempted, but the patient died six hours later. Preoperative and postmortem roentgenograms are reproduced illustrating the lesions found.

Fifty-nine diverticula were found in the jejunum and three in the duodenum, mostly between the layers of the mesentery. They appeared to decrease in size distally. In the smallest ones all the layers of the intestine were present, but in the large ones the muscularis externa was absent at the apex of the pouch. As both true and false diverticula were thus represented in the same patient, it would be less confusing simply to designate all lesions of this type as pulsion diverticula. Jejunal diverticula are very rare and usually do not cause symptoms, as in this case, as death was due to postoperative paralytic ileus and obstructive jaundice caused by a gallstone in the common duct. Diverticula are most frequently found accidentally on postmortem examination. Occasionally, after roentgen study, the lesions are thought to be gastric, owing to overlapping diverticular shadows of the small intestine. This difficulty has been noted previously with duodenal diverticula alone.

Three years ago Crohn, Ginsburg and Oppenheimer described a new disease of the small intestine, which they termed "regional ileitis." Since they called attention to this condition a number of reports on the subject have appeared, greatly amplifying the knowledge and broadening the conception of the disorder. Three articles were published in the *American Journal of Digestive Diseases and Nutrition* during 1934, which give an excellent picture of a new clinical syndrome.

Under the title "The Broadening Conception of Regional Ileitis," Crohn [47] reports 3 cases to illustrate that involvement of the intestine is much more widespread than the original designation of the disorder implies. The first patient had eight laparotomies between 1917 and 1934, without the exact cause of the trouble being ascertained. Appendectomy, intestinal resection and repair of fecal fistulas had been performed. Under Crohn's direction a ninth operation was carried out with resection of 152 cm. of small and large intestine, and the patient made an uneventful recovery. According to the pathologic report on the specimen removed there were "annular ulcerations with nonspecific, chronic inflammation of the ileum; no tuberculosis in the specimen submitted."

47. Crohn, B. B.: Broadening Conception of Regional Ileitis, Am. J. Digest. Dis. & Nutrition **1**:97, 1934.

It is emphasized that in three years the author has seen between 30 and 40 cases of the condition under discussion and that it is not rare. Surgeons should be cognizant of this fact. Symptoms suggesting appendicitis warrant close scrutiny of the coils of the lower portion of the ileum at operation. External fistulas of the abdominal wall ultimately occur and also spontaneous intestinal fistulas, which tend to heal after excision of the ileum. Peculiarly enough, fistulas of the ileum do not include the bladder.

In Crohn's second case of ileitis the condition was diagnosed roentgenographically. The patient complained of a constant mild diarrhea for two years. The first impression was of nontropical sprue, as there were hyperchromic anemia and hypoproteinemia with edema. Roentgen examination of the gastro-intestinal tract revealed the lower portion of the ileum to be irregular, and rounded shadows suggesting ulceration or small polyps were scattered widely in the ileum and in the lower portion of the jejunum. At operation 60 cm. of thickened and inflamed ileum was resected. The patient died ten days later. On the lower portion of the resected specimen diffuse ulcerating inflammation was observed. Higher up the lesion became alternating and scattered, involving the lowest portion of the jejunum as well. This case is interesting clinically because it is an instance of ileitis devoid of pain and pathologically because it is the first encountered by Crohn in which the "regional ileitis" had involved the lowermost portion of the jejunum.

In the third case Crohn termed the condition familial ileitis, as he had seen a boy of 14 with the condition, and subsequently the sister of this boy, 32 years old, was operated on for the same condition. The pathologic specimens obtained in both instances were characteristic of regional ileitis. The occurrence of these 2 cases in one family may be purely accidental, may have significance as to a congenital predisposition or may be due to a transmissible causative agent in this disease.

Under the name chronic ulcerative enteritis, Corr and Boeck [48] report an additional case belonging to the group of regional ileitis. The authors believe that this original term is not sufficiently comprehensive and that chronic cicatrizing enteritis is not exact, as it applies only to a late stage of the disease. The basic pathologic process is ulceration, and the chronicity produces a picture not unlike chronic ulcerative colitis.

The case was remarkable in that during the six years of the course all four of the different clinical phases mentioned in the literature were presented. Intestinal symptoms and cramps during the first year led to appendectomy, at which time the intestine was said to have been

48. Corr, P., and Boeck, W. C.: Chronic Ulcerative Enteritis, Am. J. Digest. Dis. & Nutrition **1**:161, 1934.

"reddened and diseased." The second phase of chronic ulcerative enteritis was represented by the same symptoms, with alternating diarrhea and mild constipation, recurring periodically during the next four years. The patient became an invalid. She had received much antiamebic therapy, as it was reported that amebas had previously been found in the stools. Attacks of severe abdominal pain with vomiting and an increase in the diarrhea suggested the development of the later phase of stenosis with obstructive symptoms. An operation for suspected intestinal obstruction was performed. Rectovaginal and abdominal fistulas formed, representing the fourth phase of the disease. The patient died of inanition. Pathologically, the striking features were that the terminal portion of the ileum was free from lesions; all but about 3 feet (91 cm.) of the small intestine was involved; the presence of pseudopolyposis surrounded by ulcerating areas was similar to that reported in cases of chronic ulcerative colitis, and the discovery of active inflammation indicated continued activity of the disease. A possible relationship of amebiasis to the underlying cause of the disease is mentioned.

This same type of disorder is intensively studied by Brown, Bargen and Weber [49] in a report entitled "Chronic Inflammatory Lesions of the Small Intestine (Regional Enteritis)." The authors are impressed by the fact that inflammatory ulcerative disease in the jejuno-ileocecal coil or regional areas of the colon pathologically is indistinguishable from that in the terminal portion of the ileum and that the involvement appears to be a clinical and not a pathologic entity. Their detailed report of the clinical and pathologic features comprises a study of 18 patients recently observed.

The disorder may occur at almost any age and is twice as common in the male as in the female sex. In half the cases the ileum alone was involved. At operation the lesions were remarkably similar. An inflammatory process involving all the layers of the intestine and rather sharply localized in area, associated with hypertrophy suggesting a stiff rubber tube, were universally noted. Most of the patients had been ill for years, and 10 had undergone previous operations, mostly for appendicitis. An abnormal condition of the ileum or colon had been noted in 6 patients, thought to be tuberculosis, Hodgkin's disease or intestinal inflammation of unknown etiology.

The most predominant complaint was pain, for which none of the patients could find any constant relief. Diarrhea was the chief complaint in only a third of the cases, but in general the stools were loose

49. Brown, P. W.; Bargen, J. A., and Weber, H. M.: Chronic Inflammatory Lesions of Small Intestine (Regional Enteritis), Am. J. Digest. Dis. & Nutrition **1**:426, 1934.

and watery, with much urgency and cramping and without visible blood. Vomiting was marked in 9 cases. The situation and character of the lesion seemed to be a factor in this symptom. Recurrent fever appeared in 10 cases, but no rise in temperature was ever noted in the other 8. Loss of weight was the striking feature in a majority of the cases. The authors were impressed by the paucity of physical findings. Emaciation and moderate anemia were usually the only objective signs. No definite leukocytosis occurred.

From a roentgenologic point of view, it is important to visualize the results of the pathologic changes which produce mural thickening with consequent narrowing of the intestinal lumen, stiffening and shortening of the involved portion and destruction of mucosa. These changes are readily revealed but demand close scrutiny of each segment by multiple roentgenoscopic observations of the descending opaque meal and careful investigation of the terminal portion of the ileum after it has been distended by reflux of the opaque enema through the ileocecal valve. Interpretation of the findings requires extreme caution. The differential diagnosis of regional ileitis involves chiefly appendicitis in the early stage and intestinal tuberculosis in all stages. The presence of tuberculosis could not be established in any of the cases despite a careful search in each. "Inflammatory lesion of the bowel" was the preoperative diagnosis in 8 of the 18 cases.

Treatment essentially is surgical. Entero-anastomosis proved sufficient to relieve some patients, but resection of the diseased segment is usually necessary. The end-results of operation are often remarkably good and in some instances may be designated as a complete cure.

LARGE INTESTINE

Scholz [50] has made an exhaustive and illuminative study of the problem of chronic appendicitis. After a relatively brief survey of the general subject, the author observes that the problem may best be solved by the investigation of three questions of prime importance: 1. Is local tenderness, as ascertained roentgenoscopically, the only reliable sign of appendicitis? And what is the diagnostic status of the other so-called signs? 2. What rôle may roentgenology play in differential diagnosis, and to what extent may it reliably serve as a means for preventing unnecessary operations? 3. Are anatomic findings or therapeutic results the best criteria for the correctness of the diagnosis of chronic appendicitis?

Several interesting series of cases of appendicitis are compared, correlating the clinical, roentgen and anatomic findings. The findings in

50. Scholz, T.: The Solution of the Roentgen Diagnostic Problem in Chronic Appendicitis, Am. J. Roentgenol. **31**:792, 1934.

these series are also compared to the findings in cases of other abdominal conditions and also to findings in a series of normal persons. The conclusions seem warranted. Scholz states that roentgenology is the best diagnostic method in chronic appendicitis, and that its main value lies in the differential diagnosis from other important lesions which may simulate it. The roentgen examination must be made by a competent roentgenologist. The roentgen diagnosis is based on a single sign, namely, local tenderness as elicited by palpation over the visualized region of the appendix. All other so-called roentgen signs are of no diagnostic value. Chronic gross anatomic changes occur in an appreciable number of clinically normal persons, and microscopic anatomic changes are found in practically every adult appendix. Anatomic changes, therefore, cannot be taken as a reliable criterion for the correctness of the diagnosis of chronic appendicitis. A much better criterion is the therapeutic result.

The recent outbreak of amebiasis in Chicago has stimulated medical thought on the general subject of intestinal ulceration. Felsen [51] gives a complete description of ulcerative disease of the intestine under the title "Practical Etiological and Clinical Consideration of Intestinal Ulceration with Especial Reference to Amoebic Dysentery, Bacillary Dysentery and Idiopathic Ulcerative Colitis." The virtue of this report lies largely in the fact that it correlates the general knowledge of a variety of conditions which are usually considered independently and that it simplifies the practical problem which confronts the average physician as to how to differentiate the various types of intestinal ulceration. A few points are worthy of review.

As pathogenic bacteria can pass through healthy intestinal mucosa, ulceration of the intestine cannot be due solely to local invasion by living bacteria. In bacillary dysentery the lesions are probably due to the excretion of toxins through the intestinal wall and they may be compared to the lesions in mercury and arsenic poisoning. On the other hand, ulceration due to direct local action on the intestinal wall is best exemplified by infection due to Endamoeba histolytica. Ulcers may also be "trophic" or embolic, and in cases of neoplasms they are essentially due to central necrosis. Their location in the intestine will have considerable bearing on the types of symptoms produced. Felsen has included some diagrams on the distribution and character of lesions in cases of ulcerative disease of the large intestine and terminal portion of the ileum which are highly instructive.

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51. Felsen, J.: Practical Etiological, Pathological and Clinical Consideration of Intestinal Ulceration, with Especial Reference to Amebic Dysentery, Bacillary Dysentery and "Idiopathic" Ulcerative Colitis, Am. J. Digest. Dis. & Nutrition **1**:297, 1934.

The general symptoms of bleeding, mucus and pus in the stool, tenesmus, abdominal pain and diarrhea are presented largely on a physiologic basis. The salient features of the major diseases causing intestinal ulceration are presented, but nothing particularly new is included.

Bargen,[52] in an article entitled "Chronic Ulcerative Colitis: Trends in Its Present Day Management," discusses the forms of therapy available and their relative value, on the basis of eleven years' experience with 1,472 cases. Rest is extremely important, just as in other chronic conditions, such as tuberculosis. Immunization by serums or vaccines is strongly advocated, and repeated courses of injections should be carried out. Such a procedure has proved the greatest single item in preventing recurrence of the disease. Transfusions of blood are of great value in selected cases. The diet should not be too greatly restricted. Adequate amounts of foods digested almost entirely in the small intestine should be given. A table of a desirable dietary regimen is presented. No drugs are specific, but a few are of value in symptomatic therapy. All foci of infection must be removed. Intestinal irrigations not only are not helpful but may actually be harmful. Surgical procedure, such as ileostomy, should be avoided, as the risk of the operation is great and the end-results disappointing.

Carcinoma is the commonest tumor of the large intestine. Sarcoma occurs less frequently. These two forms of malignant process and adenomatous polyps represent the majority of new growths of this region. However, a number of other tumors, usually benign, may occur and produce constitutional symptoms or obstructive phenomena. As the clinical picture they produce is usually thought to be due to carcinoma, a patient may be denied adequate treatment on the erroneous assumption that the condition is malignant and nothing beneficial can be accomplished.

As these uncommon tumors of the large intestine may have to be considered in the differential diagnosis of any given case, Bargen and Dixon [53] briefly describe them and their incidence. Fibroma is extremely rare. Eight cases have been observed at the Mayo Clinic, and the history of 1 case is reported. Tumors of pure muscle are exceedingly rare. These myomas have a tendency to recur after excision and to become malignant. Adenomyoma of the sigmoid colon usually develops in relatively young women secondary to pelvic disease but has appeared in men. Angioma is the rarest type of tumor found in the large intestine

52. Bargen, J. A.: Chronic Ulcerative Colitis: Trends in Its Present-Day Management, Am. J. Digest. Dis. & Nutrition **1**:190, 1934.

53. Bargen, J. A., and Dixon, C. F.: The Uncommon Tumors of the Large Intestine, Am. J. Digest. Dis. & Nutrition **1**:400, 1934.

and is probably congenital. Lipoma, except for adenoma, is the most frequently encountered benign tumor of the gastro-intestinal tract. It develops in older patients and may produce obstruction. The clinical differentiation from cancer is difficult. Cholesteatoma, dermoids and teratoma have all been reported. In a few cases, cysts of the cecum have been described. Endothelioma may arise in the rectum proper, but through early invasion of the spinal cord the symptoms are predominantly neurologic.

The treatment of all these lesions is surgical, and highly satisfactory results are frequently obtained.

The outbreak of amebiasis in Chicago in the summer of 1933 and the consequent dissemination of infected persons to all parts of the United States stimulated a hitherto unapproached interest in this parasitic infection in this country. The medical literature of the next year clearly shows how unfamiliar the majority of physicians were with the clinical manifestations and methods of diagnosis of a disease which is of daily occurrence in the tropics and is well known to physicians practicing there. Most of the papers consist of reviews of already established facts and reports of cases appearing locally and add little to the basic knowledge of infection by E. histolytica. Such a reemphasis of this subject is desirable; so a few reports of amebiasis are abstracted.

"Amebiasis and Amebic Dysentery" is the title of an excellent article by Craig,[54] who is a recognized authority in this field of medicine. It is a general review, emphasizing many points applicable to the problems raised by the presence of this parasitic infection in most cities. Craig states that unfortunately the term amebic dysentery has become synonymous with amebiasis. It should be clearly understood that the term "amebiasis" means the invasion of the tissues of man by E. histolytica and the term "amebic dysentery" means a symptom complex characterized by a bloody mucoid diarrhea which may occur as one of the clinical manifestations of amebiasis. The first is common in the United States; the second is rare and is not a disease entity but a part of the picture of amebiasis.

Although the geographic distribution is world-wide, wherever sanitation and personal hygiene are poor, amebiasis is prevalent, whether in the tropics or in the temperate zone. The vast majority of people in this country infected with E. histolytica do not have dysentery. The incidence of infection in the United States may be conservatively estimated as between 5 and 10 per cent of the population. This makes amebiasis a most serious public health problem, particularly as all untreated or improperly treated persons with amebic diarrhea become

54. Craig, C. F.: Amebiasis and Amebic Dysentery, Am. J. Digest. Dis. & Nutrition **1**:4, 1934.

carriers of the cysts of the parasite, making them potential sources of infection to others. The disease is spread through a contaminated water supply, by the use of human excretion in the fertilization of vegetable gardens, by the contamination of food and drink by the droppings of flies and by the contamination of food and drink by handlers of food who are carries of the ameba. Strains of E. histolytica apparently do not differ in virulence, but the infection is more likely to assume a severe form under conditions greatly depressing natural human resistance, such as those which existed in the early days of the Philippine insurrection.

The pathologic process of amebiasis is well recognized. It is noteworthy that marked amebic ulceration may exist in the intestine of man without producing symptoms of severe diarrhea or dysentery. The symptomatology of the disease is most likely to be represented by a host of gastro-intestinal complaints and disturbances of the nervous system rather than by the spectacular symptoms of "amebic dysentery." The exact incubation period of the dysentery is unknown but averaged sixty-four and eight-tenths days in 4 volunteers experimentally infected. The impression that fever never occurs is incorrect, as the temperature may vary between 100 and 102 F. in the severe cases. Fulminating types of amebic dysentery are rare. In addition to the usual physical signs in the abdomen, tenderness and pain in the hepatic area always indicate the presence of hepatitis and possible commencing formation of an abscess in the liver. Slight anemia and leukocytosis are present, but Craig states that eosinophilia has not occurred in his experience.

Physicians are much handicapped in making the diagnosis of amebiasis and amebic dysentery, because at present comparatively few laboratory technicians and physicians are capable of differentiating the five different species of ameba living in the human intestine. An accurate diagnosis demands the demonstration of E. histolytica in the feces of the patient. A simple microscopic preparation of an unstained specimen of the stool is successful in demonstrating the parasite in the vast majority of cases of acute amebic dysentery. Identification of the cysts may require stained preparations, or culture methods may be employed in doubtful cases. The complement-fixation test cannot be used alone in diagnosis but is highly accurate.

A most important prophylactic measure is the routine examination of handlers of food and their proper treatment, but facilities permit this to be done on only a small scale at present. Treatment as a rule is highly satisfactory. Carbarsone, formyl meta-amino-para-hydroxy-phenyl arsinic acid, or vioform will clear up all but the most chronic infections. Craig emphasizes that emetine should never be used for the treatment of carriers but is most valuable in the control of dysenteric symptoms.

Brown [55] has presented the history of 5 cases illustrating certain atypical types of amebiasis. The first patient was hospitalized for bronchopneumonia, and on the tenth night began to pass bright red blood in the stool. Despite repeated transfusions he died. At necropsy ulcerated areas were noted in the cecum and rectum. Smears from the ulcers showed E. histolytica. Such a massive hemorrhage from the large intestine is rare in amebiasis. The second patient presented symptoms and signs of subacute appendicitis. At operation the appendix seemed normal, but the colon was involved in a diffuse inflammatory process. A subsequent examination of the stool revealed E. histolytica. In the third case there was a palpable mass in the right lower quadrant, and proctoscopic examination revealed large ulcerated areas throughout the rectum and sigmoid. An opaque enema revealed a filling defect involving the cecum. Two examinations of the stool failed to disclose any parasites. Antiamebic therapy was instigated; the cecal mass disappeared, and the ulcers cleared up. Tumefactive masses caused by E. histolytica are not common and may well be confused with carcinoma.

The fourth patient had complained of bloody diarrhea for two years, and weakness and anemia were marked. Examinations of the stool gave negative results. Proctoscopic and roentgen signs of chronic ulcerative colitis were present. Many forms of therapy had been unavailing. On the first examination of the stool the specimen was almost alive with E. histolytica. All the symptoms cleared up rapidly with antiamebic therapy. This case of ulcerative colitis proved to be definitely parasitic in origin. The fifth patient had a pelvic abscess, and the condition improved with antiamebic therapy. A parasitic origin of the abscess was not proved, but it was assumed that an amebic ulcer had ruptured into the pelvis.

55. Brown, P. W.: Certain Atypical Types of Amebiasis, Am. J. Digest. Dis. & Nutrition **1**:10, 1934.

Book Reviews

Chirurgie du pancréas. By P. Brocq and S. Miginiac. Price, 75 francs. Pp. 427, with 74 illustrations. Paris: Masson & Cie, 1934.

The authors have completed an excellent monographic exposition of the injuries to, and surgical diseases of, the pancreas. The book is written in an admirable style with no tinge of lucubration, and the various surgical disorders of the pancreas are treated systematically in the accepted textbook fashion. The abundant but compendious observations on the histories of cases appropriately demonstrating the diverse clinical manifestation of each disease deserve unmitigated approbation. Although the illustrations in themselves are surprisingly deficient in artistic excellence, nevertheless they are adequately elucidative and sufficiently representative. Showing a keen sense of proportion, the authors have devoted over half the volume to the more common acute and chronic inflammatory diseases and allocated the remainder to traumas, cysts, syphilis, tuberculosis, lithiasis, fistulas, malignant tumors, and anomalies of the pancreas.

In the discussion of pancreatic injury the authors call attention to its apparent rarity in observation and to the actual infrequency in diagnosis. They opine that the explanation lies in the fact that: (1) injury to an organ so deeply situated is nearly always accompanied with associated lesions of such severity as to result in a fatal termination before time for surgical intervention; (2) because of technical difficulties, the examination of the pancreas during an emergency laparotomy may not be sufficiently thorough to reveal a wound of the pancreas. They make the bold statement that the preoperative diagnosis of a wound of the pancreas has never been made. This is more readily comprehended after one reads their chapters dealing with diagnosis.

As a matter of fact, the diagnosis of surgical diseases of the pancreas in general is wofully unsatisfactory. Although in recent years rapid progressive strides have been made toward a better understanding of the pathologic alterations of the physiology of this vital organ, the clinical manifestations are not sufficiently well defined and the laboratory and roentgen technics are not adequately developed to be of commensurate diagnostic value.

Apropos of the pathogenesis of acute pancreatitis, the authors succinctly but thoroughly discuss the vascular and the better accepted canalicular theories. They are of the opinion that this condition rarely, if ever, occurs in a normal gland. Although acute pancreatitis can be produced experimentally in normal glands of animals by the injection of various substances into the canal and by ligation of vessels, these are intensive methods. However, in an abnormal gland or one chronically diseased these exciting factors need not be so intensive. They believe that undoubtedly there are multifarious causes and discuss the possibility of a primary vascular injury, the rôle of infection, the more recently introduced allergic theory and the older theory of occasional activation of the ferments of the pancreatic secretion.

Particular emphasis is laid on the necessity of differentiating true from false cysts in order to institute rational surgical measures. As the latter have no true wall, it is useless and dangerous to attempt extirpation, which is the method of choice for the former, in which there is a true wall and in which a line of cleavage can be found. Marsupialization or incision and drainage suffice in the treatment of false cysts.

A brief discussion of aberrant pancreas and annular pancreas comprises the closing chapter on anomalies. The former is of particular interest to the surgeon, aside from its rarity, because of its confusion clinically and pathologically with peptic ulcer. It usually occurs as a reddish-yellow or brown, indurated plaque in the neighborhood of the pylorus on the stomach or duodenum and may be easily mistaken for an ulcer. The treatment is simple excision.

Although slight partiality is manifested in the citations and the appended bibliography is arranged in a rather slipshod fashion, nevertheless the latter is up to

date. The book is heartily recommended to those having an easy knowledge of French, because to be of value it requires a thorough study.

Grundzüge der pathologischen Physiologie. By Hans Lucke. Price, 6.60 marks. Pp. 195. Berlin: Julius Springer, 1934.

This book is published, as the title implies, to bring out the principal facts of pathologic physiology in a brief, concise fashion. Lucke has kept the needs of the student primarily in mind in providing a short survey of the field of pathologic physiology in a form which omits most of the confusing details and controversial aspects. The book thus supplies an opportunity for the unfamiliar reader to grasp a general understanding of the field in a short time, so that he may be oriented when breaking into the more detailed works and literature. No pretense is made at treating the subject exhaustively.

Lucke considers his subject in the usual systematic way under the major headings of metabolism of foodstuffs, total metabolism, mineral and water metabolism, vitamins and hormones and then considers the various systems, as the hematopoietic, respiratory, circulatory, renal, gastro-enteric and nervous, as well as the regulation of the body temperature and the problems of infection, immunity and allergy. Under these headings the groundwork for further more elaborate consideration is laid down in typical, terse, German style. Because of the book's purpose, no doubt, some of the newer advances in the mechanisms of disease, especially those of controversial nature, are entirely omitted or given a position of reduced importance and little emphasis. This is true of the recent work on the relationship of the anterior pituitary gland to sugar metabolism, of hyperparathyroidism and especially of the cortical extracts of the adrenal gland and sodium chloride metabolism in Addison's disease. Fat metabolism is little more than mentioned, a fact which does not reflect on the author's neglect but indicates that present knowledge of the mechanisms and pathologic physiology of fat metabolism is very meager. There are no illustrations or diagrams, nor is there a bibliography.

The reviewer recommends the book heartily for the purpose indicated. It is, of course, of limited value as a source book and reference manual.

Diseases of the Chest. By J. Arthur Myers. Edited by Morris Fishbein. Price, $3. Pp. 385, with 62 illustrations. New York: National Medical Book Company, Inc., 1935.

This book from the pen of a recognized authority on tuberculosis and diseases of the chest fulfils very well the hopes of the reviewer. Particularly instructive are the chapters on tuberculosis, of which the author has been a close student for many years. Much of the material in this book is not readily available in general texts, and it should prove a useful guide to the practitioner who is interested in diseases of the chest.

News and Comment

CENTRAL SOCIETY FOR CLINICAL RESEARCH

The Eighth Annual Meeting of the Central Society for Clinical Research will be held at the Drake Hotel in Chicago on Friday and Saturday, November 1 and 2. The meetings are open to all who are interested in clinical medicine.